

# Cerebrospinal fluid pressure and glaucoma

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The relationship between cerebrospinal fluid pressure (CSF-P) and glaucoma has aroused great interest in recent years. Before this development, elevated intraocular pressure (IOP) had long been considered as the major risk factor for the development and progression of glaucomatous optic nerve damage.<sup>1</sup> However, numerous studies have shown that there is a relatively large number of patients with typical glaucomatous optic neuropathy (normal-tension glaucoma, NTG) in whom IOP measurements have always been in the normal range (<21mmHg).<sup>2</sup> Thus, several questions arise. Why do NTG patients develop glaucoma in the absence of high IOP? Are factors other than IOP contributing to the pathogenesis of NTG?

As early as the 1970s, Volkov<sup>3</sup> pointed out that CSF-P could be a counter-pressure to IOP as well as pathogenically associated with glaucomatous optic neuropathy. In a similar manner, Yablonsky *et al.*<sup>4</sup> postulated that an abnormally low CSF-P around the optic nerve could be the reason for barotraumatically-induced optic nerve damage in primary open-angle glaucoma (POAG) with normal IOP. However, it was not until recently that retrospective studies by Berdahl *et al.*<sup>5,6</sup> and prospective studies by us<sup>7,8</sup> both found that CSF-P is lower in POAG patients. Moreover, the CSF-P data in POAG with normal IOP from another study done by Jaggi *et al.*<sup>9</sup> also reviewed a lower CSF-P.

Although the studies mentioned above providing evidence of low CSF-P in NTG seemingly resolved the better part of the IOP dilemma, the following questions remain:

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## **1. Although lumbar CSF-P is low in NTG patients, is their optic nerve subarachnoid space CSF-P low?**

The assessment of CSF-P in clinical studies was based on single lumbar CSF-P measurements, but not on a measurement of the CSF-P in the subarachnoid space (SAS) of the optic nerve. Whether lumbar CSF-P can represent CSF-P in the optic nerve SAS remains unknown. Since a direct measurement of orbital CSF-P is invasive and not acceptable in clinical practice, a 3T-MRI-based imaging technology was developed to measure optic nerve SAS width as a surrogate for optic nerve subarachnoid CSF-P. A study of 39 POAG patients, in which 21 patients had normal pressure (IOP < 21 mmHg), 18 patients had high pressure (IOP > 21 mmHg), and 21 subjects comprised the control group, found that optic nerve SAS width was significantly narrower in the normal-pressure group than in the high-pressure group or the control group.<sup>10</sup> This result demonstrated that patients with glaucomatous optic nerve damage and normal IOP had an abnormally narrow subarachnoid CSF space around the post-laminar optic nerve suggesting a low CSF-P or, as a corollary, a high trans-laminar cribrosa pressure difference (TLPD).

In addition to the clinical evidence, it remains important to illustrate the relationship among lumbar CSF-P (LCP), brain CSF-P (ICP), and optic nerve subarachnoid CSF-P (ONSP). Eight dogs were used to measure these pressures simultaneously. The results found that the pressures were different with  $ICP > LCP > ONSP$ , but correlated with each other ( $P < 0.001$ ). The trans-lamina cribrosa pressure gradient (TLPG) was highest for IOP-ONSP, lower for IOP-LCP, and lowest for IOP-ICP ( $P < 0.001$ ). During CSF shunting, ICP gradually decreased in a linear fashion together with ONSP (“ICP-dependent zone”). However, when ICP fell below a critical breakpoint, ICP and ONSP became uncoupled and ONSP remained constant despite further ICP decline (“ICP-independent zone”).<sup>11</sup> We interpret this as a sign of CSF communication arrest between the intracranial and optic nerve SAS. This may be caused by obstructions of either CSF inflow through the optic canal or outflow into the intra-orbital cavity.

## **2. Can low CSF-P induce glaucomatous optic neuropathy?**

Yang *et al.*<sup>12</sup> conducted an experimental investigation in monkeys to further explore the potential association between an abnormally low CSF-P and glaucomatous optic nerve damage. Four monkeys received a lumbar-peritoneal shunt to reduce CSF-P, while five control monkeys underwent the same procedure but with the shunt remaining closed. Follow-up examinations included regular measurements of IOP and CSF-P, confocal laser scanning tomography of the optic nerve head and retinal nerve fiber layer, and fundus photography. Four eyes of two study-group monkeys developed a continuous loss of retinal nerve fiber layer, and one eye of a third monkey showed a splinter-like disc hemorrhage during the follow-up. The

other three eyes in the study group and all eyes of the monkeys in the control group remained unchanged. It was concluded that the chronic reduction of CSF-P led to optic nerve damage in some monkeys with experimental and chronic reduction in CSF-P. Whether optic nerve damage corresponded to glaucoma remained unclear.

### 3. Can we measure CSF-P for glaucoma patients clinically?

In the context of an increased TLPD in the pathogenesis of POAG, one may infer that the diagnostic and therapeutic pattern for POAG patients may be changed. Therefore, it seems essential to examine TLPD in POAG patients. However, lumbar puncture for POAG patients is currently controversial and not applicable in a clinical setting. Although some non-invasive ways of measuring ICP have been developed, the accuracy and efficacy of these methods remains dim. More importantly, orbital CSF-P is the key to TLPD, but ethical concerns regarding the invasiveness of the procedure required for direct measurement has stopped us from conducting this type of research. Finding a non-invasive way to measure orbital CSF-P seems essential and applicable.

Based on 3.0T MRI, the Intracranial and Intraocular Pressure Study Group (iCOP) developed an algorithm for a non-invasive measurement of intracranial CSF-P with MRI-assisted optic nerve SAS measuring with intraclass correlation coefficients (ICCs) of 0.87.<sup>13</sup> Subsequently, an easier formula to estimate CSF-P without measuring optic nerve SAS was established by means of multivariate analysis ( $\text{CSF-P [mmHg]} = 0.44 \times \text{BMI [kg/m}^2\text{]} + 0.16 \times \text{Diastolic Blood Pressure [mmHg]} - 0.18 \times \text{Age [Years]} - 1.91$ ). It confirmed previous investigations that had also reported on associations between higher BMI and higher CSF-P.<sup>14,15</sup> Applying the formula in an independent test group revealed that the measured CSF-P ( $12.6 \pm 4.8$  mmHg) did not differ significantly ( $P=0.29$ ) from the calculated CSF-P ( $13.3 \pm 3.2$  mmHg). We then applied this formula to the population-based Beijing Eye Study, which included 3468 individuals, and Central India Eye and Medical Study, which included 4711 individuals; the results showed that in POAG, but not in angle-closure glaucoma, calculated TLPD versus IOP showed a better association with glaucoma presence and amount of glaucomatous optic neuropathy.<sup>16,17</sup> These results support the notion of the potential role of low CSF-P in the pathogenesis of POAG.

TLPD imbalance may play an important role in the pathogenesis of glaucomatous optic nerve damage. Mathematical model research is vital and must be continued to elucidate the downstream mechanisms of increased TLPD in glaucomatous optic neuropathy. Given that a rational and precise procedure for diagnosing and managing POAG based on TLPD is not currently applicable, obstacles and problems should be conquered and intensive investigations should be continuous. Clinically, IOP reduction still seems the most applicable way of decreasing TLPD and treating POAG patients. It may be of interest to find a way to increase CSF-P non-invasively.

Moreover, it is also important to estimate the target TLPD, which may be more reasonable than IOP alone.

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