Cerebrospinal Fluid Pressure and Glaucoma

Intracranial pressure may hold the key to understanding why IOP plays a major role in the development of glaucoma.

BY JOHN BERDAHL, MD

Glaucoma is not well understood. It is an optic neuropathy of unknown etiology that results in a characteristic pattern of visual field loss and changes to the optic nerve. Elevated IOP is a well-known risk factor for the development of glaucoma, but it is not always present, such as in cases of normal-tension glaucoma (NTG). Furthermore, an individual with high IOP may not develop glaucoma. For example, only a small percentage of people with ocular hypertension (OHT) ultimately develop glaucoma.[1] The mechanism through which IOP contributes to optic nerve damage remains speculative despite immense research efforts.

In addition to IOP, the optic nerve is exposed to intracranial pressure (ICP) as it is surrounded by cerebrospinal fluid (CSF) in the subarachnoid space immediately posterior to the lamina cribrosa. Because the lamina cribrosa separates these two pressurized regions,[2] the decrease in pressure that occurs across the lamina cribrosa (IOP - ICP) is known as the *translaminar pressure difference*. The average IOP is 16 mm Hg, and the average ICP is 12 mm Hg, resulting in a small, posteriorly directed pressure difference across the lamina.[3] If this disparity became larger due either to an elevation in IOP or a reduction in ICP, the imbalance could result in glaucomatous changes.

WHAT IS PRESSURE?

The term *intraocular pressure* is a misnomer. IOP is typically considered to be the pressure inside the eye, but this is mostly incorrect. A better term would be *transcorneal pressure difference*. Applanation tonometry applies a force outside the eye that equals the force inside the eye (across the cornea) according to the Imbert-Fick principle. This measurement (IOP) is unrelated, however, to the absolute pressure in the eye, because absolute pressure varies significantly with the barometric pressure that is experienced simultaneously by all tissues of the body. Interestingly, the absolute pressure in the eye is of little significance, whereas the transcorneal pressure difference (IOP) does matter in glaucoma. This makes sense when one considers that it is differences in pressure that generate forces. The pressure difference across the cornea (IOP) may be important as a surrogate for the pressure difference across the optic nerve head (IOP - ICP). Instead of comparing the pressure inside the eye to atmospheric pressure outside the eye, as with IOP, perhaps clinicians should compare the pressure inside the eye to the ICP.

A DISRUPTION OF HOMEOSTASIS

Aqueous humor and CSF represent the two circulating fluids of the nervous system, and they share many

(Illustrations by Kathleen A. Rowland.)

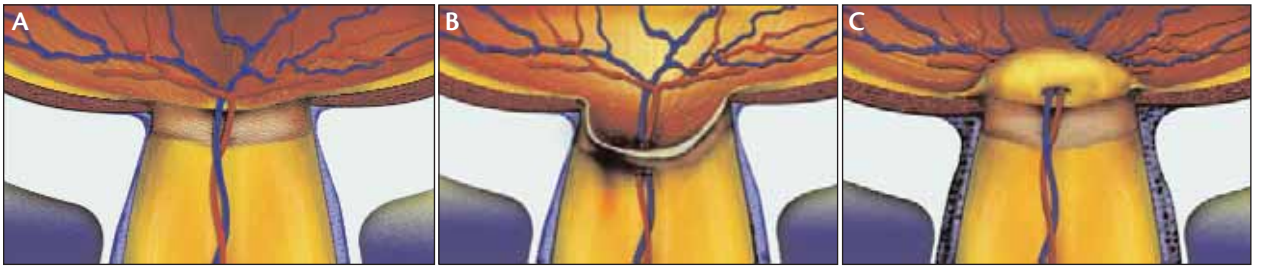

Figure 1. The relationship of IOP to ICP. A normal nerve shows a balance between IOP and ICP (A). A glaucomatous nerve exhibits cupping as a result of an IOP that is higher than the ICP (B). A swollen nerve results from an ICP that is higher than the IOP, such as in pseudotumor cerebri or ocular hypotony (note the swollen CSF space) (C).

similarities. Both are produced by carbonic anhydrase-catalyzed reactions and generally represent an ultrafiltrate of blood. In the normal state, the similarity in average IOP and ICP results in a small translaminar pressure difference. Increasing that difference alters the homeostatic balance and generates great posteriorly directed force at the level of the lamina cribrosa, resulting in glaucoma (Figure 1). ICP can affect the optic nerve in diseases such as pseudotumor cerebri, in which the ICP becomes higher than the IOP, resulting in a swelling of the optic nerve head. Similar swelling occurs in ocular hypotony, where the translaminar pressure difference is altered not by elevated ICP but low IOP. Either way, the optic nerve swells secondary to an alteration of the translaminar pressure difference.

If the balance between IOP and ICP is the critical factor, then patients with OHT who do not develop glaucoma may be protected by an elevated ICP, whereas patients with NTG may develop glaucoma because of an abnormally low ICP.

MECHANISM OF ACTION OF GLAUCOMATOUS OPTIC NEUROPATHY

A higher translaminar pressure difference may lead to abnormal function and nerve damage due to changes in axonal transport, deformation of the lamina cribrosa,

Discussion: Cerebrospinal Fluid Pressure in the Pathogenesis of Glaucomatous Optic Neuropathy

BY JOST B. JONAS, MD

The article by John Berdahl, MD, focuses on the potential pathogenic role of an abnormally low orbital cerebrospinal fluid (CSF) pressure in the development of glaucomatous damage to the optic nerve, particularly in patients with normal-tension glaucoma (NTG). Dr. Berdahl discusses several anatomical and physiological aspects of the optic nerve head region and cites previous investigations by Morgan and others.[1-8] The published discussion of this topic dates back more than 30 years.[9]

As a term, *intraocular pressure* (IOP) is convenient but a misnomer, because we measure the transcorneal pressure difference. The importance of understanding the difference between so-called IOP and true IOP is illustrated by the following example. If eyes A and B have a so-called IOP of 20 and 40 mm Hg, respectively, the relative difference in true IOP between these eyes is not 100%, as one might easily assume. Instead, it is only 2.5%: 760 mm Hg (surrounding atmospheric pressure) plus 20 mm Hg (transcorneal pressure difference) in eye A versus 760 mm Hg plus 40 mm Hg in eye B.

The transcorneal pressure difference, however, is not of the utmost importance for the optic nerve, which is located at the watershed (or pressure shed) between the compartments of the intraocular space and the orbital CSF space. Of greater significance is the difference in pressure between the intraocular compartment (so-called IOP) and the orbital CSF space (so-called brain pressure, if one assumes that the CSF pressure in the brain equals the CSF pressure in the orbital optic nerve meninges). Because these compartments meet at the lamina cribrosa, the pressure difference between them may be termed the *translamina cribrosa pressure difference*, assuming that the CSF pressure in the orbital optic nerve meninges equals the tissue pressure in the optic nerve just behind the lamina cribrosa. In situations of very low orbital CSF pressure, however, studies by Morgan have shown that the tissue pressure in the retrolaminar optic nerve tissue can be higher than the CSF pressure in the optic nerve meninges.[10]

Based on animal studies by Morgan, anatomical findings, and theoretical considerations, Dr. Berdahl and colleagues recently conducted a retrospective analysis of patients' charts, which revealed a significantly lower lumbar CSF pressure among individuals with NTG than those with high-IOP glaucoma or healthy subjects. Further, they reported that the amount of glaucomatous damage to the optic nerve correlated with the difference in transcorneal pressure (IOP) and lumbar CSF pressure (presumably, orbital CSF pressure values).[11,12] As a corollary, subjects with ocular hypertension had an abnormally high CSF pressure.

The findings of Dr. Berdahl and colleagues were recently confirmed by a prospective study,[13] which additionally suggested that, in normal subjects, the CSF pressure is related to the systemic arterial blood pressure (conventionally measured at the upper arm) and the IOP. According to several population-based studies,[14,15] the IOP is also related to the systemic arterial blood pressure so that the pressure in all three fluid-filled compartments (ie, the intraocular space, the CSF space, and the arterial blood compartment) are related to each other. This idea raises the possibility of

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explaining and combining the findings of previous well-conducted, hospital-based studies on patients with NTG. In this research, patients with NTG characteristically had a low systemic blood pressure, suggesting a perfusion disorder as the reason for optic nerve damage. All morphological studies on the appearance of the optic nerve head in patients with vascular optic neuropathies, however, had shown typical differences between these eyes and those with glaucoma.[16,17] Now, however, if one assumes that the low blood pressure in patients with NTG is associated with an abnormally low CSF pressure—leading to an abnormally high translamina cribrosa pressure difference—then one may assume that the low blood pressure, through its association with a low CSF pressure, leads to barotraumatic optic nerve damage at the lamina cribrosa. This action would be similar to when the IOP is high and the orbital CSF pressure is normal.[3]

These considerations and the landmark studies by Dr. Berdahl and colleagues[11,12] may show that, at least theoretically, it is necessary to discuss and further explore the potential role of low orbital CSF pressure in the pathogenesis of glaucomatous damage to the optic nerve. Despite all presumably logical interpretations of the findings thus far, one must bear in mind that the hypothesis of low orbital CSF pressure as pathogenically important for glaucoma has not yet been proven at a scientifically acceptable level of evidence. If further studies reach similar conclusions, however, one of the therapeutic consequences could be an avoidance of systemic carbonic anhydrase inhibitors. These drugs lower CSF pressure as well as IOP, again pointing to some similarities in the physiology (and pathophysiology) of the IOP space and the orbital CSF pressure compartment.

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altered blood flow, or a combination thereof. Clearly, in glaucoma, axonal transport is reduced at the lamina cribrosa,[4-8] which is thinner and posteriorly bowed in these diseased eyes.[9-11] The thinness of the lamina cribrosa may be a critical factor in the optic nerve's susceptibility to the translaminar pressure difference. A thinner lamina cribrosa would necessitate a higher translaminar pressure gradient (the pressure difference across a specific distance) and create a steeper path that retrograde axonal transport must traverse—much like swimming up a waterfall. Recent data indicate that the lamina thickens (but is still posteriorly displaced) at the earliest detectable stage of experimental glaucoma in monkeys.[12,13] This response may represent the body's efforts to protect itself from a high pressure difference.

Ocular blood flow may be inseparably intertwined with ICP. Both IOP and ICP appear to be affected by blood pressure.[14] If systemic hypotension results in decreased CSF production and a lower ICP, the risk of glaucoma would presumably increase, which might explain why nocturnal hypotension appears to be a risk factor for NTG. On a smaller scale, differences in IOP and ICP occurring at the optic nerve head may lead to localized areas of decreased blood flow and, ultimately, glaucomatous damage.

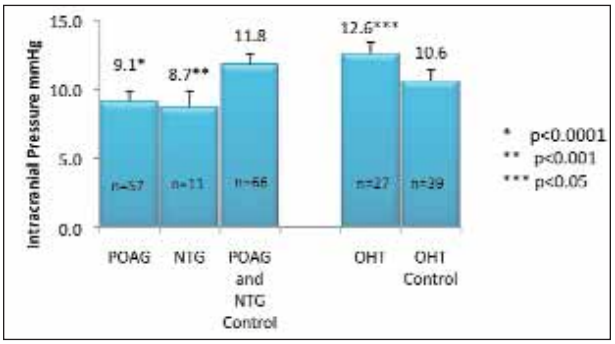

Figure 2. ICP in patients with POAG, NTG, and OHT and in controls.

THE DATA

My colleagues and I retrospectively reviewed the charts of 62,468 patients who had lumbar punctures at the Mayo Clinic over a 20-year period and identified 189 who met our inclusion criteria, including a complete eye examination by an ophthalmologist.[15,16] The ICP was significantly lower in patients with primary open-angle glaucoma (POAG) and NTG and was significantly higher in those with OHT when compared to that of individuals without glaucoma (Figure 2). For perspective, the 3- to 4-mm Hg difference in ICP between patients with and without glaucoma is similar to the difference in IOP between patients with POAG and controls in large population-based studies.[17,18] Additionally, a difference of 4 mm Hg in IOP can mean the difference between stability and glaucomatous progression.[14,19,20] The apparently small divergence between groups therefore may have large implications.

OTHER CONSIDERATIONS

Many factors continue to limit physicians' understanding of ICP's role in glaucoma. Positional changes affect both ICP and IOP, leading to alterations in the translaminar pressure difference,[21-26] and the orbital tissue pressure may transmit forces that influence the retrolaminar CSF pressure.[27,28] "Snapshot" measurements of the IOP and ICP may not accurately represent the long-term variations in pressure that are probably more important in a chronic disease like glaucoma. Animal models, mathematical models, and prospective studies should help to clarify the mechanisms of glaucoma.

CONCLUSION

A pressure imbalance between the two circulating fluids of the nervous system may be the cause of glaucomatous damage to the optic nerve. The ICP is lower than normal in POAG and NTG and elevated in OHT. These findings suggest that an elevated ICP in OHT may counterbalance the high IOP, thus potentially preventing or slowing glaucomatous damage to the optic nerve. Conversely, a reduced ICP in patients with NTG may increase their risk of developing glaucoma. ❑

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