

Author Response: Deficient Optic Nerve Sheath Occlusion in NTG Patients: Optic Nerve Damage Due to Translaminar Pressure Imbalance, Glymphatic Failure, or Both?

We would like to extend our gratitude to Wostyn for his comments and interest in our article, "Optic Nerve Subarachnoid Space Posture Dependency—An MRI Study in Subjects With Normal Tension Glaucoma and Healthy Controls."¹ We found indications of altered cerebrospinal fluid (CSF) behavior in subjects with normal tension glaucoma (NTG) in an upright position and focused on the mechanical trans-lamina cribrosa pressure difference (TLCPD) theory. Wostyn et al. suggest that there may be a connection between the mechanical theory of NTG highlighted in our article and the glymphatic theory for glaucoma,² which provides another potential explanation for glaucoma pathophysiology that is linked to the failure of the occlusion mechanism of the optic nerve sheath.

We found Wostyn's hypothesis intriguing and would like to add some complementary thoughts. As described by Wang et al.,³ the glymphatic system of the eye is primarily thought to be a pathway for efflux of ocular fluid through the lamina cribrosa into the optic nerve (ON), thereby assisting the clearance of potentially toxic waste products produced in the metabolically active retina. They also showed that the beta-amyloid from the eye accumulates in ON perivenous spaces and indicated that the subsequent transport from the ON is through the ocular nerve sheath.³ We speculate that this transport could be assisted by the CSF flow that enters through the arterial perivascular spaces of the ON,^{3,4} similar to the described pathways of brain glymphatic flow.⁵ Interestingly, TLCPD drives the transport of fluid and toxic metabolites from the ocular system to the ON,³ supporting that a non-collapsing optic nerve sheath (ONS), causing high TLCPD, would actually increase the transport with potential accumulation in the venous perivascular spaces. At the same time, the input to the ON glymphatic flow from the CSF side is potentially reduced by the decreased intracranial pressure (ICP), potentially causing the impaired flow also identified in glaucoma by Mathieu et al.⁶ In essence, this means that a dysfunctional ONS collapse in upright position would result in a change in the balance between clearance of metabolites from the ocular compartment and the flushing inflow of CSF from the subarachnoid space. It is highly speculative, but such an imbalance could cause a toxic environment in the ON causing

neurodegeneration and thus be a part of an NTG etiology. The hypothesis motivates further research on the actual driving forces of the CSF glymphatic flow and the confirmation of a dysfunctional ONS collapse together with beta-amyloid accumulation in the ON of NTG patients.

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