Twists and turns of ocular glymphatic clearance – new study reveals surprising findings in glaucoma

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remains poorly understood, as well as its implication in the variations observed in diabetic patients.

All these parameters modifying choroidal thickness must be taken into account. As such, one should consider the healthy fellow eye when dealing with a unilateral disease or a healthy patient matched for a wide range of parameters (age, blood pressure, autonomous dysregulation, etc.) for diseases affecting both eyes.

In conclusion, current knowledge on CT parameters has not yet given all its clues. It gives hope to better understand its real value and role in the pathophysiology of diabetic retinopathy. Further studies should be done in diabetic patients, which correlate systemic autonomous dysregulation of the cardiovascular system to the modification of CT.

References


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Twists and turns of ocular glymphatic clearance – new study reveals surprising findings in glaucoma

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Editor,

The central nervous system (CNS) is largely devoid of functional lymphatic vessels, apart from within the meningeal lining (Louveau et al. 2015). The brain can eliminate cellular waste and excess interstitial fluid from deep in the parenchyma using paravascular spaces facilitated by the water channel aquaporin-4 (AQP4) (Iliff et al. 2012). The hallmark of the brain glymphatic system is the movement of small cerebrospinal fluid and solutes along arteries driven by hydrostatic pressure, convective interstitial fluid movement facilitated by AQP4 on astroglial endfeet and perivascular spaces of the retina and optic nerve. Small tracer molecules like amyloid-beta and radio-labeled potassium entered retinal ganglion cell (RGC) axons and the perivascular spaces of the retina and optic nerve head (ONH) before being cleared by the antegrade glymphatic pathway. Larger dextrans were blocked from posterior outflow both by the intact glial lamina in mice and the more developed lamina cribrosa in rats. Directional water and small solute movement inside axons are distinct from and sometimes have a different direction from the ATP-driven axonal transport along microtubules (Beaulieu 2002). We found that RGC axons appeared to use the hydrostatic pressure gradient to promote fluid and solute delivery across the ONH, where the axons take a sharp turn before exiting the eye. Raised intracranial pressure (ICP) abrogated the intraxonal tracer movement along the optic nerve, whilst lowering ICP or stimulating pupil movement increased it. The lamina cribrosa appears to have not only an anatomical function of supporting axon bundles, but also a vital physiological role as a hydrostatic barrier redirecting fluid and solute movement into axons and the perivascular spaces at the ONH and retrolaminar nerve (Wang et al. 2020). One of our most surprising findings was that two distinct animal models of glaucoma were both characterized by excessive and misdirected glymphatic
In fact, excessive extracellular tracer and may promote wash out of straints, as is seen in papilloedema, accommodated due to space movemements across the ONH cannot be anteriorly located routes. Large fluid magnitude lower than clearance via outflow is likely to be orders of tous eyes is unknown. Glymphatic exits the eye via this posterior clear-modation. The amount of fluid that tial functional coupling with accom-

movement across the ONH in glauco-matous mice masked an impairment of intra-axonal tracer clearance. The lam-ina no longer re-directed fluid into axons but allowed passage via large defects in this barrier. We speculate that slowing of intra-axonal tracer clearance in our glaucoma models reflects build-up of metabolic waste like amyloid beta within RGC, leading to dysfunction and cell death.

As the eye is considered an extension of the CNS, glaucoma is sometimes described as ocular dementia. A key finding in our study is that glaucoma-tous damage to the lamina barrier impairs the clearance of small and potentially neurotoxic solutes such as amyloid beta via a novel glymphatic pathway. Several important questions remain. What other small solutes and ions are dependent on the ocular glymphatic clearance pathway for effi-
cient transport? Can we develop diagnostic tracers to study this pathway in a clinical setting and modulate trans-port to delay or prevent optic nerve diseases like glaucoma? Further character-

ization of the ocular glymphatic system could be vital in the development of new diagnostics and treat-ments for several potentially blinding conditions.

References


phatic system dysfunction. Fluids Barriers CNS 12: 16.