Optic Disc Edema in Astronauts from a Choroidal Point of View

Peter Wostyn; Charles R. Gibson; Thomas H. Mader

INTRODUCTION: Optic disc edema has been well documented in astronauts both during and after long-duration spaceflight and is hypothesized to largely result from increased pressure within the orbital subarachnoid space brought about by a generalized rise in intracranial pressure or from sequestration of cerebrospinal fluid within the orbital subarachnoid space with locally elevated optic nerve sheath pressure. In addition, a recent prospective study documented substantial spaceflight-associated peripapillary choroidal thickening, which may be a contributing factor in spaceflight-associated neuro-ocular syndrome. In the present article, based on the above, we offer a new perspective on the pathogenesis of microgravity-induced optic disc edema from a choroidal point of view. We propose that prolonged microgravity exposure may result in the transudation of fluid from the choroidal vasculature, which, in turn, may reach the optic nerve head, and ultimately may lead to fluid stasis within the prelaminar region secondary to impaired ocular glymphatic outflow. If confirmed, this viewpoint would shed new light on the development of optic disc edema in astronauts.

KEYWORDS: choroidal interstitial edema, choroidal thickening, intracranial pressure, ocular glymphatic system, optic disc edema, spaceflight-associated neuro-ocular syndrome, trans-lamina cribrosa pressure difference.

Wostyn P, Gibson CR, Mader TH. *Optic disc edema in astronauts from a choroidal point of view*. Aerosp Med Hum Perform. 2022; 93(4):396–398.

Ophthalmic abnormalities, including optic disc edema (ODE), globe flattening, choroidal folds, and hyperopic shifts in refraction, have been observed in astronauts during and after long-duration spaceflight (LDSF).[6,9] The term "spaceflight-associated neuro-ocular syndrome" (SANS) is currently used to describe these findings.[6] Given the impact of SANS on astronaut visual health, investigating SANS mechanisms is a high priority for the National Aeronautics and Space Administration (NASA). Here we present a new viewpoint, according to which choroidal volume changes may contribute to SANS-associated ODE.

Two basic mechanisms have been offered to explain astronaut ODE. First, microgravity-induced cephalad fluid shifts may cause venous stasis in the head and neck.[9] This stasis may cause impairment of cerebrospinal fluid (CSF) drainage into the venous system and cerebral venous congestion, both of which could increase intracranial pressure (ICP).[9] A second hypothesis suggests that microgravity-induced ODE results from a localized CSF pressure increase within the tightly confined, orbital subarachnoid space, producing a type of optic nerve sheath compartment syndrome, with or without a rise in cerebral CSF pressure.[6,9] The end result of either mechanism is increased CSF pressure within the orbital subarachnoid space, stasis of axoplasmic flow, axonal swelling, and ODE.[9]

A recent prospective study by Macias and colleagues[8] reported prominent increases in astronaut peripapillary choroidal thickness that were detected early during LDSF, persisted throughout the mission, and required 45 to 90 d on Earth to recover to preflight levels. It is hypothesized that cephalad fluid shifts during microgravity exposure cause venous congestion in the head and neck, resulting in a rise in vortex vein pressure, decreased choroidal drainage, a relatively stagnant pooling of blood in the choroid, and subsequent choroidal expansion.[9] This abrupt increase in choroidal volume may account for the sudden

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This manuscript was received for review in October 2021. It was accepted for publication in January 2022.

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DOI: https://doi.org/10.3357/AMHP.6010.2022

spike in intraocular pressure (IOP) documented during transient microgravity exposure.[9] Other factors, such as increased episcleral venous pressure, may also impact IOP during microgravity exposure.[9] As regards the effect of spaceflight on IOP, limited in-flight data suggests an initial spike in IOP on entering microgravity followed by a return to preflight baseline values after a few flight days, possibly resulting from diminished aqueous volume or other compensatory mechanisms.[9]

We previously hypothesized that increased resistance to venous drainage from the eye during spaceflight could result in the transudation of fluid from the choroidal vasculature, ultimately resulting in some degree of choroidal interstitial edema.[14] Greenwald and colleagues[2] proposed a similar mechanism in which chronically elevated hydrostatic pressure within the arterial or venous vasculature may promote capillary filtration across the permeable choroidal vasculature and gradually produce an accumulation of extravascular fluid and choroidal expansion. Thus, besides the rapid pooling of blood in the choroid that occurs on entry into microgravity, the chronic accumulation of choroidal interstitial fluid (ISF) may add to the reported increase in peripapillary choroidal thickness during and after prolonged microgravity exposure.[14] This circumferential zone of peripapillary interstitial choroidal expansion may contribute to ODE in astronauts. Indeed, based on a finite element model, Feola and colleagues[1] hypothesized that the effects of a circumferential zone of choroidal compression at the optic nerve head (ONH) level could create an anterior compartment syndrome in the prelaminar area and add to the magnitude of the prelaminar axon swelling. As discussed below, we propose a second mechanism according to which microgravity-induced transudation of fluid from the choroidal vasculature may reach the ONH, ultimately leading to fluid stasis within the prelaminar region secondary to impaired ocular glymphatic outflow.

Traditional lymphatic vessels subserve many important functions in the human body, including maintenance of fluid homeostasis.[5] However, although a recent study provided evidence of lymphatic-like structures in the human choroid,[5] the existence of choroidal lymphatics is still under debate.[4] Furthermore, if such lymphatic drainage systems exist, perhaps microgravity exposure leads to lymph stasis. Taking this into account, we believe that some choroidal fluid may reach the ONH through the border tissue of Elschnig. In support of this notion, Tso and colleagues[12] demonstrated that the border tissue of Elschnig is permeable. Using horseradish peroxidase as a tracer for electron microscopy and the normal rhesus monkey as the experimental animal, the authors demonstrated that in certain regions of the ONH, tracer from the choriocapillaris reaches the ONH through the border tissue of Elschnig from the adjacent choroidal tissues. The tracer was observed to penetrate freely into the extracellular space surrounding the axons of the ONH.[12] Interestingly, Nedergaard and colleagues[13] recently identified a novel "ocular glymphatic system" for removal of fluid and metabolites from the intraocular space via the proximal optic nerve in rodents. Small tracer molecules like amyloid-beta entered retinal ganglion cell axons and the perivenous spaces of the retina and ONH before being cleared by the anterograde glymphatic pathway.[13] This newly discovered ocular glymphatic pathway, enabling intra-axonal and perivenous efflux at the ONH, might represent an alternative way to deal with choroidal ISF outflow. Nedergaard and colleagues[13] further showed that efflux via this pathway is driven by the trans-lamina cribrosa pressure difference (IOP-ICP). A rise in ICP was shown to inhibit the ocular glymphatic outflow. Importantly, these data also suggest that a rise in orbital CSF pressure, which is assumed to occur in microgravity due to mildly elevated ICP and/or CSF compartmentalization, would directly inhibit this ocular glymphatic outflow. Therefore, in space, it seems likely that this glymphatic pathway may fail to provide for a rapid peripapillary choroidal ISF turnover, which we believe may at least partially account for the finding of some degree of ODE consistently associated with SANS. Specifically, although ophthalmic imaging demonstrates Frisen grade ODE in only 16 to 19% of crewmembers during LDSF,[11] ODE as quantified by optical coherence tomography has been documented in approximately 70% of crewmembers.[7]

The recent discovery of an "ocular glymphatic system" could also provide one possible explanation for the slow recovery of peripapillary choroidal thickness in astronauts after spaceflight as reported by Macias and colleagues.[8] Indeed, Nedergaard and colleagues[10] noted that this posterior ocular glymphatic route likely clears fluid in much lower amounts compared to anteriorly located routes. Therefore, although the choroidal vascular engorgement may suddenly be abolished upon returning to Earth, it may take many weeks for peripapillary choroidal ISF to exit the eye via the ocular glymphatic clearance route, which may account for the prolonged peripapillary choroidal expansion reported in astronauts following LDSF.

Hearon and colleagues[3] recently documented, in a terrestrial supine bed-rest study, that the nightly 8-h use of a lower body negative pressure (LBNP) device attenuated the increase in both choroid area and volume as compared to controls. The authors hypothesized that LBNP reinstated a footward fluid shift that mitigated choroidal expansion. An important question is whether the similar use of a LBNP device on the International Space Station that temporarily reverses impaired hydrostatic gradients would impact the magnitude and speed of resolution of peripapillary choroidal expansion as compared to controls. Furthermore, future research is required to provide additional insight regarding the relative contribution of peripapillary choroidal thickening to microgravity-induced ODE. If confirmed, this would shed new light on the development of ODE in astronauts.

ACKNOWLEDGMENTS

Financial Disclosure Statement: The authors have no funding to report and declare no conflicts of interest.

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Erratum

Since publication of the following article, the editor has become aware of additional disclosures that were not included with the submitted manuscript.

Tsung A, Jupiter D, Jaquish J, Sibonga J. *Weekly bone loading exercise effects on a healthy subject's strength, bone density, and bone biomarkers*. Aerosp Med Hum Perform. 2021; 92(3):201–206.

1. The first author of the study (Ann Tsung, M.D., M.P.H.) was the subject of the study.
2. The first author used the OsteoStrong equipment free of membership fee for this study, a value of $763.
3. Dr. John Jaquish is the Science Advisor for OsteoStrong and received his Ph.D. from Rushmore University, certified/accredited in accordance with UK National Standards, but whose accreditation is not recognized in some jurisdictions.