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EDITORIAL

A potential compensatory mechanism for spaceflight associated neuro-ocular changes from microgravity: current understanding and future directions

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The unique environment of space (including microgravity) exposes long-duration spaceflight (LDSF) participants to numerous physiologic challenges [1, 2]. In preparation for future crewed missions to the Moon and Mars, the National Aeronautics and Space Administration (NASA) Human Research Program has compiled a list of health risks associated with spaceflight [1]. One such risk, labelled as "red" for the highest priority, is a collection of neurologic and ophthalmic findings termed spaceflight associated neuro-ocular syndrome (SANS) [1–3]. The clinical and imaging findings of SANS include optic disc oedema, globe flattening, retinal nerve fibre layer thickening, chorioretinal folds, hyperopic shifts, and cotton-wool spots [4–6]. About 70% of all crewmembers who have participated in LDSF have demonstrated one or more of these neuro-ocular signs [6]. While the precise mechanism of SANS remains ill-defined, a major contributing factor is thought to be the cephalad fluid shift and subsequent venous congestion that occurs upon exposure to microgravity during LDSF [4–7].

Despite this redistribution of fluid towards the head, chronic elevation of intra-ocular pressure (IOP) has not been observed in astronauts on long-duration space flights [4–6]. A transient spike in IOP occurs as astronauts enter microgravity, followed by a decrease over the period of days to clinically normal levels [5, 6, 8]. This normalization of IOP during spaceflight occurs despite a sustained cephalad venous fluid shift [9]. A proposed explanation is a compensatory decrease in aqueous volume [5].

The conventional aqueous outflow pathway accounts for approximately 75–90% of aqueous outflow, in which aqueous humour flows through the trabecular meshwork (TM) into Schlemm's canal (SC) before exiting the eye via episcleral veins [10]. According to the simplified Goldmann equation, factors affecting IOP include aqueous humour production, facility of trabecular outflow, and episcleral venous pressure [11]. As histologic studies indicate a strong correlation between outflow capacity and dimensions of outflow pathway sites, alterations in the morphology of the conventional outflow pathway could be a major contributor to the normalization of IOP in microgravity [12].

Advancements in ocular imaging allow for visualization of SC and the TM in vivo. Ultrasound biomicroscopy (UBM) enables imaging of anterior segment structures in high resolution using a higher frequency transducer than that of traditional ophthalmic ultrasound (a 50–100 MHz vs 10 MHz). With UBM, significant decreases in both the coronal diameter of SC and thickness of the TM in patients with primary open angle glaucoma (POAG) have been demonstrated [13]. Anterior segment optical coherence tomography (AS-OCT) is another newer modality that can produce cross-sectional images at an even higher resolution than UBM [14]. With these modalities, new avenues of investigation into physiologic changes in anterior segment structures have become available.

AS-OCT has been used to evaluate the therapeutic effect of medical and procedural treatments for terrestrial POAG. An increase in SC surface area by >90% was observed after treatment with a topical prostaglandin prodrug (travoprost), a medication approved to lower IOP in POAG, with maintenance of SC surface area seen up to 84 h following eye drop instillation [15]. In addition, laser treatments (e.g., selective laser trabeculoplasty) target expansion of SC cross-sectional area (CSA) and can decrease IOP from increased outflow facility [16, 17].

Physiologic alteration of the aqueous outflow apparatus morphology has been observed after exercise and during forced Valsalva manoeuvre. After aerobic exercise, increased TM thickness and SC CSA have been imaged with AS-OCT [18]. This alteration in morphology, and its consequent increase in trabecular outflow facility is presumed to be a response to the IOP elevation induced by aerobic exercise [19]. An additional example of a physiologic compensation for increased IOP is the increase in SC CSA observed after subjects performed a Valsalva manoeuvre, a forceful exhalation against a closed airway that is associated with an elevation in IOP [20].

A longitudinal investigation of changes in the aqueous outflow pathway during microgravity may be useful in studying SANS during LDSF. Currently, head down tilt (HDT) bed rest (HDTBR) is a terrestrial analogue to microgravity. Supine subjects in bed are tilted down to produce a cephalad fluid shift [21]. Individuals following HDT have demonstrated a similar pattern of IOP normalization over time to that observed in astronauts [22]. Using AS-OCT, Chen et al. documented a decrease in SC CSA in individuals subject to brief HDT [23]. After 15 min of 20° HDT, IOP increased significantly from 14 to 17 mm Hg, and SC CSA decreased from a sitting value of 13449 μm^2 to a posttest value of 9576 μm^2. These changes in SC CSA may reflect what occurs as astronauts enter space, which would align with the observed transient spike in IOP. Both validation of these findings in space and longer duration HDT studies on Earth would contribute to our understanding of IOP regulation.

We propose to use AS-OCT and UBM to study the anterior segment in HDTBR and SANS. Because these modalities are noninvasive and produce high resolution cross-sections of the anterior segment, they would be suited for longitudinal assessment of structural changes to SC and the TM. Previous studies have indicated that changes in the dimensions of SC and the TM are associated with changes in IOP (Table 1). Over a period of days, an increase in the dimensions of SC and the thickness of the TM may be contributing to increased aqueous outflow by

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Table 1. Summary of papers reviewed that involve anterior segment imaging of changes in conventional outflow pathway morphology.

Authors	Year	Imaging modality	Major findings	Measured IOP change	Measured SC change	Measured TM change
Chen et al. [15]	2013	AS-OCT (FD-OCT)	Instillation of 0.004% travoprost eye drops is associated with reduced IOP and increased SC dimensions.	Mean reduction in travoprost treated group of 2.23 mm Hg	Peak value of CSA increased from 2854 to 5431 μm^2 in nasal quadrants and from 2862 to 5443 μm^2 in temporal quadrants.	-
Hong et al. [24]	2013	AS-OCT (SD-OCT)	POAG is associated with decreased SC area	-	Mean SC CSA of was 13991 μm^2 in healthy controls and 11332 μm^2 in patients with POAG	-
Yan et al. [19]	2016	UBM (80 MHz)	POAG is associated with decreased SC dimensions and decreased TM dimensions	-	Mean coronal SC diameter was 44.5 μm in healthy controls and 35.7 μm in patients with POAG.	Mean TM thickness was 103.9 μm in healthy controls and 88.3 μm in patients with POAG
Skaat et al. [16]	2017	AS-OCT (ED-OCT)	Patients with POAG treated with SLT have decreased IOP and increased dimensions of SC	Mean IOP decreased from 19.8 to 14.4 mm Hg	Mean SC CSA increased from 2478 to 2682 μm^2	-
Tandon et al. [25]	2017	UBM	Paediatric patients with congenital glaucoma had a decreased diameter of SC	-	Mean meridional SC diameter was 142 μm in non-glaucomatous eyes and 65 μm in glaucomatous eyes	-
Sun et al. [20]	2020	AS-OCT	Valsalva manoeuvre is associated with an acute increase in IOP and SC area	Mean IOP increased from 15.1 to 18.8 mm Hg	Mean SC CSA increased from 7712 to 8921 μm^2	-
Yuan et al. [18]	2021	AS-OCT (SS-OCT)	Aerobic exercise is associated with a reduction in IOP and an increase in SC dimensions in both healthy controls and patients with POAG	Mean IOP was reduced from 13.04 to 12.03 mm Hg in healthy controls and from 16.82 to 14.70 mm Hg in patients with POAG.	Mean SC CSA increased from 151.8 to 198.2 pixels in healthy controls and from 80.48 to 99.2 pixels in patients with POAG.	-
Chen et al. [23]	2021	AS-OCT (ED-OCT)	15 min of 20° HDTBR is associated with increased IOP and decreased SC dimensions.	Increase from 14 to 17 mm Hg	CSA decreased from 13449 to 9577 μm^2	-

IOP intraocular pressure, *SC* Schlemm's canal, *TM* trabecular meshwork, *AS-OCT* anterior segment optical coherence tomography, *ED-OCT* enhanced depth optical coherence tomography, *HDTBR* head-down tilt bed rest, *CSA* cross-sectional area, *UBM* ultrasound biomicroscopy, *POAG* primary open angle glaucoma, *SLT* selective laser trabeculoplasty, *SS-OCT* swept source optical coherence tomography increasing trabecular outflow facility. An increase in outflow could explain the observed normalization of IOP that occurs during long-duration exposure to microgravity. Elucidation of this mechanism is also expected to provide novel insights into POAG pathophysiology, a disease with a mysterious aetiology despite being the second leading cause of blindness worldwide.

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