Gravitational Influence on Intraocular Pressure: Implications for Spaceflight and Disease

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Abstract: Spaceflight-associated neuro-ocular syndrome (SANS) describes a series of morphologic and functional ocular changes in astronauts first reported by Mader and colleagues in 2011. SANS is currently clinically defined by the development of optic disc edema during prolonged exposure to the weightless (microgravity) environment, which currently occurs on International Space Station (ISS). However, as improvements in our understanding of the ocular changes emerge, the definition of SANS is expected to evolve. Other ocular SANS signs that arise during and after ISS missions include hyperopic shifts, globe flattening, choroidal/retinal folds, and cotton wool spots. Over the last 10 years, ~1 in 3 astronauts flying long-duration ISS missions have presented with ≥ 1 of these ocular findings. Commensurate with research that combines disparate specialties (vision biology and spaceflight medicine), lessons from SANS investigations may also yield insight into ground-based ocular disorders, such as glaucomatous optic neuropathy that may have the potential to lessen the burden of this irreversible cause of vision loss on Earth.

Key Words: body position, intraocular pressure, episcleral venous pressure, space, fluid shifts, microgravity, weightlessness

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Spaceflight-associated neuro-ocular syndrome (SANS) describes a series of morphologic and functional ocular changes in astronauts first reported by Mader et al.[1] This was previously referred to as visual impairment and intracranial pressure (VIIP) syndrome because the presentation of available data was similar to terrestrial intracranial hypertension. However, because astronauts do not have documented irreversible central visual acuity loss (hyperopic shift is correctable) and because pathologically elevated intracranial pressure (ICP) remains unclear, the National Aeronautics and Space Administration (NASA) decided that SANS was a better descriptor of the changes in astronauts. Commensurate with research that combines disparate specialties (vision biology and spaceflight medicine), lessons from SANS investigations may also yield insight into ground-based ocular disorders such as glaucomatous optic neuropathy that may have the potential to lessen the burden of this irreversible cause of vision loss on Earth.

SANS

SANS is currently clinically defined by the development of optic disc edema during prolonged exposure to the weightless (microgravity) environment, which currently occurs on International Space Station (ISS) (Fig. 1). However, as improvements in our understanding of the ocular changes emerge, the definition of SANS is expected to evolve. Other ocular SANS signs that arise during and after ISS missions include hyperopic shifts, globe flattening, choroidal/retinal folds, and cotton wool spots (Fig. 1). Over the last 10 years, approximately one in 3 astronauts flying long-duration ISS missions have presented with ≥ 1 of these ocular findings. However, it is important to note that no irreversible functional change has been documented during long-duration spaceflight (up to 6 months). Thus far visual acuity is correctable with corrective lenses during spaceflight. Visual field testing has not shown reproducible visual field defects in returning astronauts. However, visual fields may not detect subtle changes present during postflight testing, and therefore, long-term follow-up of astronauts is warranted.[3] Again, this was one of the reasons that motivated the name change from VIIP to SANS. To gain more insight, electrophysiological testing targeting the pattern electroretinogram[4] and photopic negative response[5] of the ganglion cell are planned as part of future NASA-funded research studies. Thus, as NASA has limited experience with long-duration space missions, it may take some time to understand if there are any long-term functional changes to astronaut vision.

Multiple mechanisms have been hypothesized for causing SANS, including increased ICP, cephalad fluid shifts, radiation exposure retinopathy, and hypercapnia. Among these, increased ICP is a well-known cause of disc edema on Earth, but there have been no direct measures of ICP during spaceflight, and preflight comparator lumbar puncture ICP measures have not been conducted.[6] A handful of lumbar punctures have been performed during the postflight period when astronauts were readapting to a gravitational environment.[1] These were on the higher end of normal or only moderately elevated (22, 21, 28.5, and 28 cm H_2O). Consequently, the interpretation of these data is challenging. Future studies plan to directly measure lumbar puncture ICP before and after spaceflight and to determine if a relationship exists with the manifestation of

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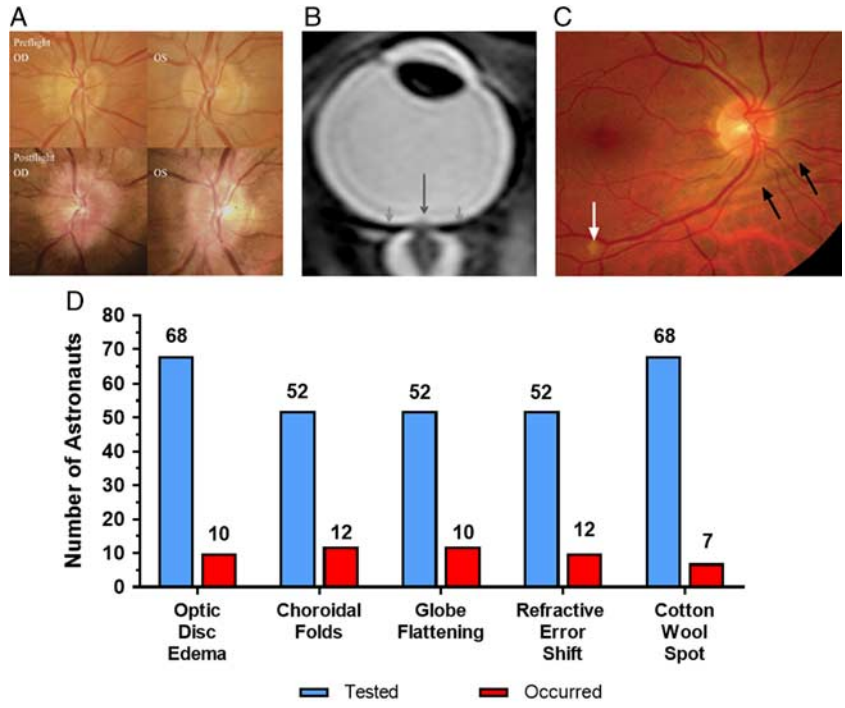

FIGURE 1. A, Photograph of disc edema after spaceflight. This finding defines spaceflight-associated neuro-ocular syndrome. B, Ultrasound showing optic nerve sheath dilatations and posterior globe flattening (arrows). C, Photograph showing choroidal folds (black arrow) and cotton wool spot (white arrow). D, Total number of US Astronauts tested for each ocular variable (blue) and the number demonstrating the finding through 2017. Optic disc edema defined as Frisèn Scale grade ≥ 1 from postflight fundoscopy images; choroidal folds visualized on fundoscopy images and/or optical coherence tomography B-scans when available; globe flattening on the basis of a subjective call from either magnetic resonance imaging or ocular ultrasound images; refractive error shift on the basis of pre to postflight change in cycloplegic refraction ≥ 0.75 D; cotton wool spot observed on fundoscopy images during or after spaceflight. Images adapted from Mader et al.[1,2] Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

ocular changes in flight (https://taskbook.nasaprs.com). Thus, among the other hypotheses, the focus of several research investigations thus far has been on the fluid shift hypothesis.

FLUID SHIFT HYPOTHESIS AND IOP

Lack of gravity causes fluids shifts. On Earth, body fluids are exposed to gravity and thus the upright posture has associated hydrostatic pressure from head to toe, with higher pressures at the lower extremities during upright posture, as compared with the level of the eye. In space and during weightlessness, the removal of the gravitational gradient leads to a headward shift of fluids, resulting in altered local tissue fluid pressures (Fig. 2).[8] Given that astronauts are unable to "stand up" during spaceflight, the headward fluid shift creates a constant and chronic stimulus that has been hypothesized to be a primary contributing factor to the development of optic disc edema. Thornton used a stocking plethysmograph to document ~2 L of fluid movement from the legs to the thorax during spaceflight.[9] Upon entering weightlessness, astronauts reported symptoms of "space adaptation syndrome," including facial edema, headaches, and dizziness.[10] Furthermore, the lack of a gravitational gradient not only shifts fluid towards the head but also decreases the fluid volume in the limbs.[9] On Earth, this concept is consistent with limb elevation above heart level as a method to reduce limb edema for various medical conditions.[11] Ultrasound images of the internal jugular vein of astronauts during short-duration spaceflight demonstrated a 40% increase in the cross-sectional area relative to the seated posture on Earth.[12] Similarly, during long-duration ISS missions, internal jugular vein volume increased by as much 200% compared with preflight supine values.[13] Taken together, these results demonstrate a robust spaceflight-induced cephalad fluid shift, but what role this plays in the pathophysiology of SANS remains an active part of multiple investigations.

Theoretically, the cephalad fluid shift that develops in weightlessness from microgravity should cause IOP to increase as a result of increased episcleral venous pressure as dictated by the Goldman equation (see the RELEVANCE TO EARTH EYE DISEASE section). Acute weightlessness induced for ~20 to 30 seconds of parabolic flight does cause ~7 mm Hg increase in IOP.[14] Similarly, after 25 minutes of weightlessness during the 8-day manned German Spacelab Mission, IOP increased by ~5 mm Hg,[15] which was similar to the 4 to 7 mm Hg increase observed during the first day on 6 Space Shuttle missions.[6] However, IOP then normalized after the first 4 days of spaceflight to values observed before the flight in the seated posture.[6] During the German-Russian MIR 10-day Spacelab D2 mission, IOP measurements were performed 15 minutes after launch and also demonstrated that IOP increased from baseline values of 10

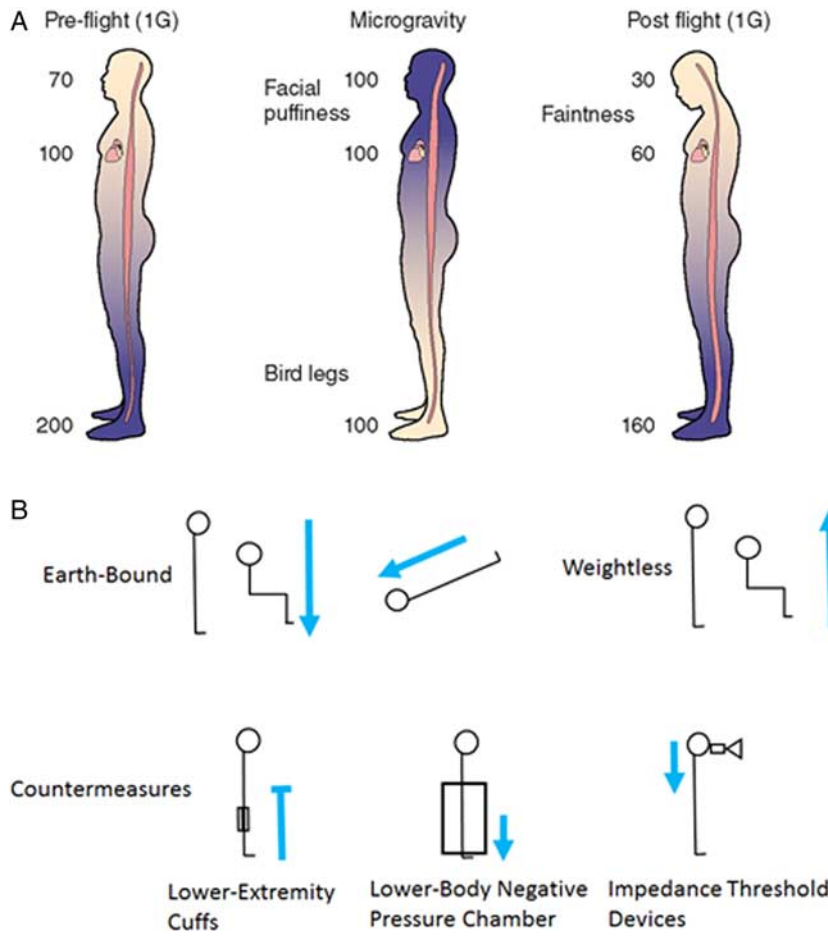

FIGURE 2. A, Preflight on Earth (1G) arterial blood pressure at the head is ~70 mm Hg, however, the pressure at the feet is 200 mm Hg. During microgravity, it is hypothesized that arterial blood pressure from head to foot is similar because of the absence of the hydrostatic pressure gradient. Postflight (1G), without the use of countermeasures, blood volume is reduced from preflight levels resulting in reduced blood pressure at head level (figure adapted from Zhang and Hargens).[7] B, On Earth, gravity directs body fluid towards the lower extremities in upright positions but towards the head in head-down tilt position. During weightlessness, in the microgravity environment of space, cephalad fluid shift is seen even in upright positions. Proposed countermeasures theoretically combat this. Lower-extremities cuffs block cephalad fluid flow under weightlessness (blue line with blunted head). Lower-body negative pressure chambers draw fluid to the lower extremities. Impedance threshold devices draw fluid into the head and in the thoracic cavity. Blue arrows denote overall body fluid flow. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

(OD) and 10 mm Hg (OS) to 23 (OD) and 22 mm Hg (OS) within the first 24 hours of the mission.[16] Again, IOP values returned to preflight baseline values by the fourth day of spaceflight.[16] IOP measured during long-duration spaceflight suggests it remains similar to preflight values throughout the duration of the mission.[6] After the return from long-duration spaceflight, IOP values were similar to preflight measures (10 to 14 vs. 10 to 16 mm Hg, respectively).[1] Thus, currently published data suggest that there is an immediate increase in IOP upon entering weightlessness, but that it normalizes to ground-based levels after a few days of flight. Chronically elevated IOP is not observed in astronauts during long-duration ISS missions. However, this normalization of IOP during spaceflight seems to occur despite a sustained cephalad venous fluid shift. These data suggest that a compensatory mechanism normalizes IOP, but this process is not yet fully understood. Moreover, because spaceflight-induced IOP changes seem to be on the order of ~5 mm Hg, future systematic investigation of IOP on ISS should use an IOP device that has high sensitivity.

On Earth, the effect of an acute cephalad fluid shift on IOP is well documented,[17–22] reproducible, and investigations regarding IOP in SANS research may provide insights into Earth-bound diseases. Indeed, inducing a cephalad fluid shift on Earth by assuming a supine or head-down tilt (HDT; ~6 to 15 degrees) body position shifts fluids towards the head as the head moves below the hydrostatic indifference point, causing an increase in IOP. It is believed that this acute posture change causes an increase in episcleral venous pressure (EVP), and this has been measured in the supine position.[23] The magnitude of IOP increase can be remarkable (~40 mm Hg in vertical head-down suspension)[24] with associated diminished retinal electrophysiological responses.[24,25] Thus, IOP change during supine sleep is likely explained in-part by alteration in body position,[18] and spaceflight data suggest that if this increase

were sustained, then the normal healthy response would be to normalize IOP. Understanding this normalization mechanism may prove useful for better treating glaucoma patients with chronically elevated IOP. Understanding the regulation of IOP during posture changes and in healthy astronauts during prolonged weightlessness may provide new insight into the long-debated role of body position IOP elevation in glaucoma.

SANS STUDIES USING HDT (CHRONIC AND ACUTE)

On Earth, HDT (chronic and acute) has been used to study fluids shifts and to replicate, study fluid shifts and to replicate, study, and develop countermeasures against many of the physiologic changes that occur in weightlessness.[26] However, until recently, SANS findings have not been observed using this spaceflight analog.[27] Previous bed rest studies allowed subjects to lift their head and upper torso during meals, and prop their head up using a pillow throughout the day and night.[27–29] This may have led to differences in the headward fluid shift compared with that which occurs during weightlessness. Further, as the environment failed to fully replicate the mild elevation in CO_2 levels that exist on ISS, a recent bed rest study was designed to limit lifting the head and to include a mild CO_2 environment. For the first time, use of strict HDT bed rest for 30 days in a mild hypercapnic environment (3.8 mm Hg ambient PCO_2) induced Frisèn grade[30] 1 or 2 optic disc edema in 5 of 11 healthy test subjects.[31] OCT images were used to quantify an average increase in the total retinal thickness of 39 μm around the nerve after 30 days of HDT bed rest.[31] This was a ~4 to 5 times greater change than what has been observed after 70-day HDT bed rest with a standard pillow in a normal ambient environment.[27] Six months after completion of the trial, Frisèn grade optic disc edema resolved in all cases (personal communication, Steven Laurie). Thus, this study was critically important because it created the first model of "reversible" human optic disc edema that could be used to study SANS and develop potential countermeasures for use during spaceflight. The incidence of optic disc edema during spaceflight is 16% and frequently presents with folds; however, during bedrest, 50% of the subjects presented with optic disc edema but none of the subjects developed folds (S. Laurie, personal communication, 2019). Therefore, it remains to be determined if the mechanism underlying optic disc edema during bed rest is exactly the same as that which occurs during spaceflight. Future research remains necessary to understand multiple outstanding questions, including intravenous retinal angiography to look for disc leakage, optical coherence tomography angiography (OCTA) to investigate microvascular alternations, and electrophysiological assessment of ganglion cells to determine if functional changes develop concurrently with the observed structural changes.

As SANS-like changes have only begun to be observed in chronic HDT, *acute* (short term) HDT has been useful to evaluate various SANS countermeasures. One countermeasure is lower body negative pressure (LBNP) which is a technique that applies a vacuum to the lower extremities to shift fluid away from the central circulation.[19] Although effective at translocating fluid, LBNP tethers the crew to a single location in a spacecraft and requires continuous cardiovascular medical monitoring to ensure syncope does not develop, making this countermeasure operationally challenging to implement.

Venoconstrictive thigh cuffs (VTC) are another countermeasure that applies pressure over the femoral vein to trap venous blood in the legs as a means of shifting fluid out of the upper body (Fig. 3). VTCs have been used by Russian Cosmonauts to combat space adaptation syndrome and reduce symptoms of "head congestion."[32] Although these alone may not be as successful at moving as much fluid as LBNP, they do allow the crew to move freely about the spacecraft while completing other activities for extended periods of time and do not require continuous cardiovascular monitoring, making them more operationally desirable.

At an average systemic blood pressure of 120/80 mm Hg, mean arterial pressure (MAP) is ~90 mm Hg. Thus, with single leg VTCs compressing at 50 to 60 mm Hg,

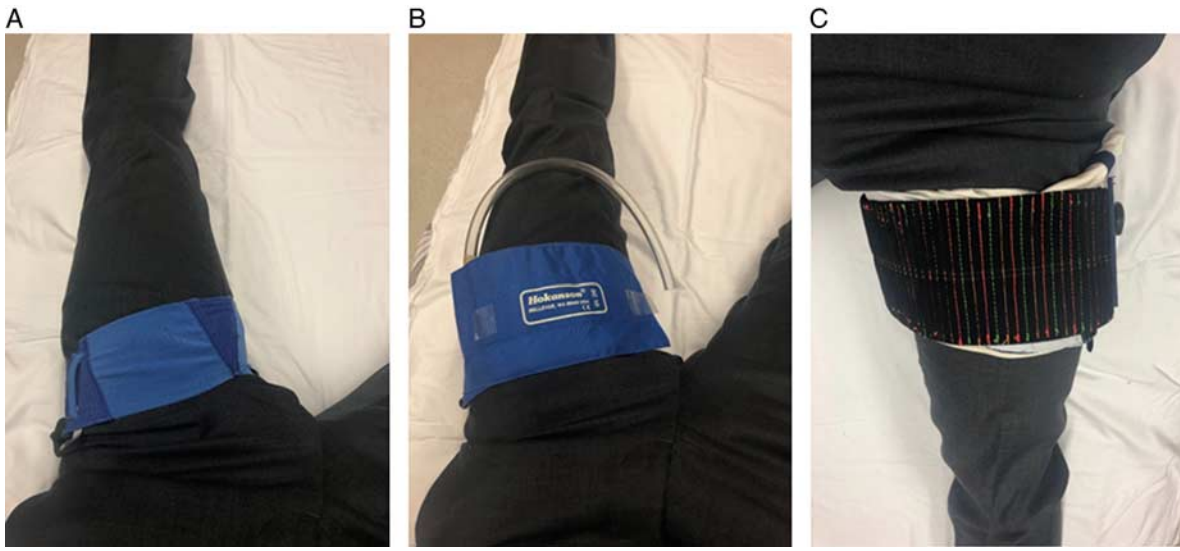

FIGURE 3. A, Photograph of Russian Bralset venoconstrictive thigh cuff device. B, Photograph of pneumatic venoconstrictive thigh cuff device. C, Photograph of mobile venoconstrictive thigh cuff device with modified width and variable pressure adjustment mechanism.

there is not enough pressure to block arterial blood flow into the lower extremities, but there is enough pressure to compress venous beds to diminish venous return to the upper body. In support of these approaches, the "Medical Flight" 1994 to 1995 experiments on the Mir space station demonstrated that use of VTCs reduced jugular vein cross-section area by 12% to 20%.[33,34] Use of VTCs in ground-based studies has demonstrated similar results of decreased internal jugular vein (IJV) diameter as well as effects on the femoral vein.[35]

Currently, 2 additional types of VTCs are under investigation. A pneumatic VTC uses an electrically driven pump to inflate a bladder to set the pressure that is automatically maintained (Fig. 3). The advantage is the ability to deliver precise and constant pressure, and the disadvantage is an electrical requirement tethering astronauts to a power source. Mobile VTCs also exist and compress the upper thigh using micro- and macro-manipulators which tighten and lock the cuff (Fig. 3). Theoretically, this should provide even greater mobility, however, a disadvantage is that it currently lacks automatic feedback mechanisms to maintain a steady compression.

Because the goal of VTCs or LBNP is to translocate fluid away from the head through the venous system and thereby reduce venous pressure at the level of the eye, the effectiveness of these countermeasures can be quantified by studying alterations to the eye that come from acute HDT. The application of LBNP during HDT has been shown to significantly lower IOP by ~2 mm Hg,[19] and we have shown the ability of both VTCs to reverse the increased IOP and subfoveal choroid thickness that develop during HDT.[20] Preliminarily, OCTA has also documented foveal avascular zone shrinkage in the HDT position that was partially reversed with VTCs.[36] Therefore, ocular endpoints like IOP exist for body position alteration-induced acute fluid shifts, and they have been useful to assess potential countermeasures on Earth. However, it is important to state again that acute HDT differs from the presumably mild chronic cephalad fluid shift experienced by astronauts on the ISS. Thus, the real purpose of these studies is to identify candidate countermeasures on Earth that could effectively reverse a headward fluid shift at the level of the eye before future studies are conducted during spaceflight.

RELEVANCE TO EYE DISEASE ON EARTH

Although these studies are illuminating for understanding and preventing SANS, they also offer potential insight into Earth-bound diseases. For example, the observation that VTCs partially reversed acute HDT-induced IOP elevation[20] may have relevance for glaucoma by raising the complex relationship between ICP, IOP, ocular blood flow, and body position.

There may be a role for ICP in the pathophysiology of SANS and glaucoma, however, the narrative is complex. Again, initially, the signs and symptoms of SANS suggested that ICP may be the initiating factor. However, with ground-based and ISS research studies complete or near completion, well-controlled and quantitative data suggest that elevated ICP may not be significant or at most just one of the potential pathophysiological mechanisms. This encouraged the name change from VIIP to SANS.[37] In glaucoma, the interplay between IOP and ICP has also gained recent attention because of both retrospective[38] and prospective[39] observations that glaucoma patients have decreased ICP.[38] Thus, decreased ICP (or increased IOP) to cause an increased translaminar pressure gradient has been postulated as an additional risk factor in glaucoma. Of course, the difference between glaucoma and SANS is the opposite speculated direction for ICP change. However, if research in either field can yield improved and potentially noninvasive ways to measure ICP or translaminar pressure gradient, this becomes an example of how investigation in 1 discipline could help the other.

Considered alone, many pivotal studies have shown that elevated mean IOP is a very important risk factor for glaucomatous optic nerve progression.[40–44] However, the mechanism behind IOP elevation damaging the nerve is not fully understood. Mechanical mechanisms have been proposed related to the pressure that is exerted on the nerve in addition to the support (or lack thereof) of nerve fibers traversing the lamina cribosa.[45,46] In contrast, blood flow theories hold that elevated IOP diminishes the ocular perfusion pressure (OPP) gradient.[47,48] OPP is the difference between the arterial pressure entering the eye and the IOP that pushes back against this. With no method to directly measure OPP, it is assessed during clinical research as the difference between adjusted MAP and IOP (OPP = adjusted MAP–IOP) (Table 1). Adjusted MAP is obtained from blood pressure taken at the upper arm followed by a mathematical correction to try to account for the distance between the arm and eye (see below). Thus, one hypothesis is that decreased OPP may cause glaucomatous optic nerve progression due either to high IOP or low arterial blood flow entering the eye.

The true importance of OPP is unclear, but the concept is tantalizing because of its constituent components. The risk factor of IOP in glaucoma is well known. Low blood pressure has also been associated with glaucomatous optic neuropathy.[47,50,51] However, attempts to directly link calculated OPP to glaucoma have been very difficult. First, the adjusted MAP is obtained from routine systemic blood pressure measurements at the arm. As the eye is >1 foot away from the arm, equations have been devised to estimate the arterial pressure entering the eye (adjusted MAP) (Table 1). These equations are nuanced by body position because in a vertical position, the eye is above the arm, and when supine, the arm and eye are at equal levels.

With all of this in mind, the weaknesses of this overall OPP approach are significant. Imagine for a moment this scenario. A theoretical eye drop medication enters the eye, traverses the vitreous, and actually alters the retinal or optic

TABLE 1. MAP Calculations and Adjustments

Parameter and Body Position	Equation
MAP	Diastolic BP+ (systolic BP–diastolic BP)/3
Adjusted MAP for arterial pressure at eye (seated)	(0.66×MAP)
Adjusted MAP for arterial pressure at eye (supine)	(0.88×MAP)
Adjusted MAP for arterial pressure at eye (head-down tilt)	MAP+7

BP indicates blood pressure; IOP, intraocular pressure; MAP, mean arterial pressure.

Adapted from Liu et al[49] and Zhang and Hargens.[7]

nerve vasculature to bring additional blood flow into the eye. The drug improved arterial perfusion and thus improved OPP without directly altering IOP. In this case, there is only 1 way to experimentally observe this finding using the above methods. *The eye drop has to increase systemic blood pressure measured at the arm*. This is obviously nonsensical, difficult to achieve, and not the actual goal.[52] Therefore, improving OPP through the arterial component of the equation is hard because the proper tools do not yet exist to demonstrate it at the level of the eye. In the future, new vasculature assessment methods such as OCTA may be useful.[53–55]

Improving OPP by altering IOP is more straightforward. It can be argued that this is exactly what is done every day in glaucoma clinics through the use of eye drops (prostaglandins and aqueous suppressants) to lower IOP. This is where HDT studies offer additional insights.[20] As discussed above, acute HDT led to increased IOP which could be considered deleterious. This risk is unclear though because HDT also increases passive arterial blood flow into the eye on the basis of gravity (see above adjusted MAP equations). Therefore, gravity's simultaneous elevation of IOP and ocular arterial blood flow could theoretically negate each other and result in minimal to no net alteration to OPP. This is also why it is unclear if solely taking a supine position at night is necessarily harmful in glaucoma despite increased IOP. However, VTCs (the SANS countermeasure discussed above) lowered IOP irrespective of body position (HDT-VTC IOP < HDT IOP) effectively decoupling IOP (and EVP) from blood flow despite body position change.

It is important to appreciate that VTCs in SANS countermeasures research were not designed to treat glaucoma. For many patients on Earth, they are not only Earth-bound but literally bed-bound because of the inability to regulate total body volume as a result of diseases such as cardiomyopathy. Regardless of the cause (dilatory, hypertrophic, or restrictive),[56] lack of cardiac forward flow can lead to pulmonary and lower extremity edema. In such cases, passive limb elevation or simple compressive stockings are used to facilitate venous return to the central circulation. This is opposite to what VTCs are intended for. Further, by slowing down venous blood flow, the theoretical risk of lower-extremity thrombus formation exists. Thus, the goal should not be to give every glaucoma patient VTCs but instead to understand the actual mechanisms through which

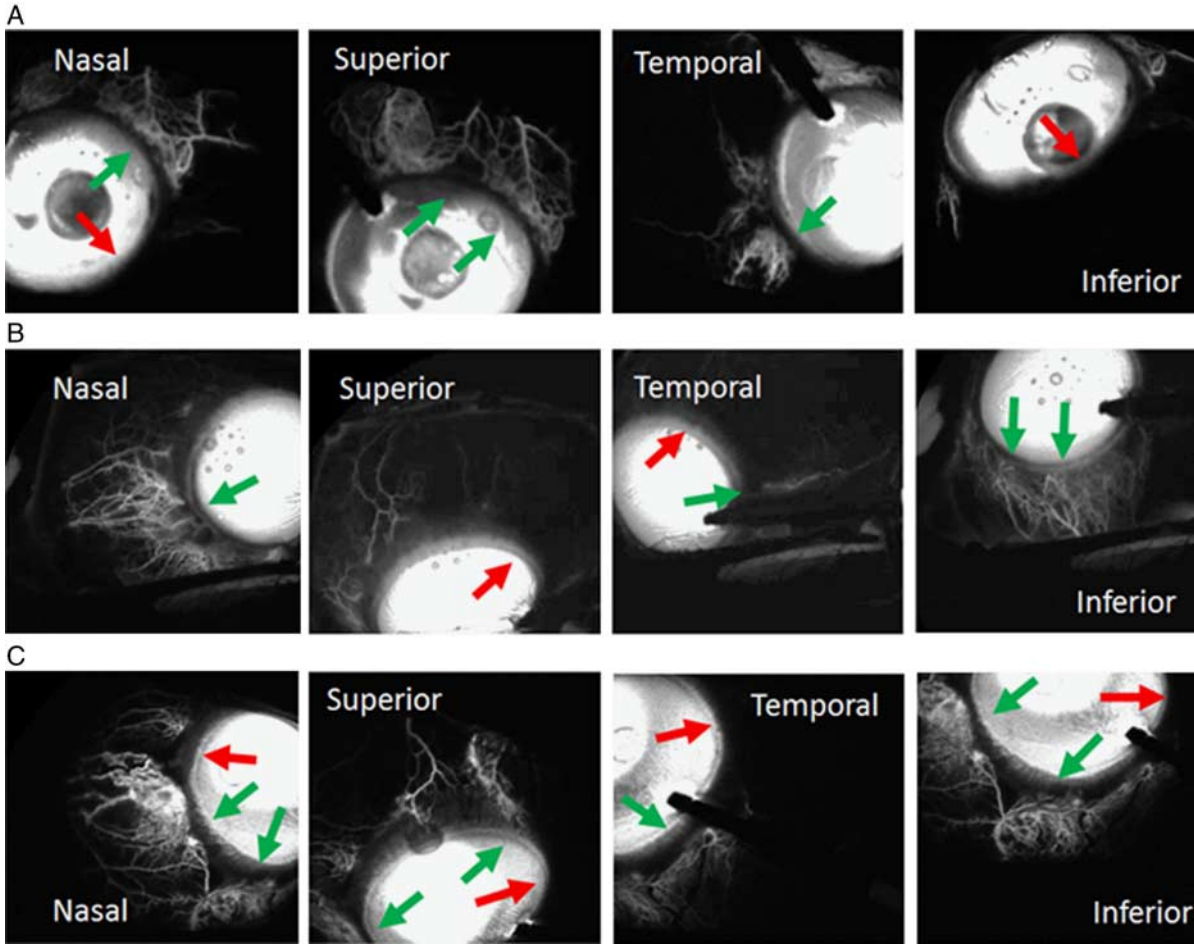

FIGURE 4. Episcleral veins. Aqueous angiography introduces fluorescent tracers into the eye followed by angiographic imaging in live human subjects, here undergoing routine clinically indicated cataract surgery. Rows (A–C) show episcleral venous patterns from 3 eyes from 3 live patients. Each row is 1 subject. Segmental patterns are seen showing regions with (green arrows) and without (red arrows) angiographic signal. It is these episcleral veins which may be impacted by body position to alter intracranial pressure or be a target for intracranial pressure lowering using cytoskeletal relaxing agents. Figure reproduced from Huang et al's[62] study with permission from author.

VTCs lower IOP. Here it seems that VTCs work by modulating EVP, and now new innovative ways can be considered to achieve the same endpoint.

The import of EVP in IOP regulation is gaining traction. IOP is determined by a balance between aqueous humor production (flow into the eye) and aqueous humor outflow (AHO) through the conventional and unconventional pathways. This process is best modeled by the modified Goldman equation[57] where $IOP = (F_{in} - F_{out})(R) + EVP$ [IOP is intraocular pressure (mm Hg); $F_{in}$is aqueous production (μL/min); F_{out} is unconventional outflow (μL/min); R is conventional outflow resistance (mm Hg×min/μL); and EVP is episcleral venous pressure (mm Hg)]. Using aqueous angiography, real-time AHO has been visualized and noted to be segmental around the limbus in multiple species including humans in both laboratory eyes and living subjects.[58–63] Aqueous angiography has demonstrated the novel finding of dynamic AHO where regions with and without baseline episcleral vein AHO can actually gain or lose flow (Fig. 4).[64,65] This means that there may be local regulation of AHO at episcleral veins which in part reflects the growing appreciation that the distal AHO pathways (including episcleral veins) play a role in IOP and possibly glaucoma. Moreover, future technological advances may enable the measurement of EVP in various body postures.

Today, new FDA-approved treatments exist that may already work by lowering EVP. Cytoskeletal relaxing agents are a new drug class including rho-kinase (ROCK) inhibitors and nitric oxide (NO) donors.[66,67] Initially, laboratory evaluation demonstrated that cytoskeletal relaxing agents lowered AHO resistance.[68,69] Focused on the trabecular meshwork (TM), these drugs mechanistically impacted TM cytoskeleton, contractility, and extracellular matrix to promote easier AHO. However, long studied in other systems, NO derivatives are also well known to vasodilate and are first-line treatments for acute coronary syndrome and vasospastic angina.[70] Decades-old animal studies have shown that NO derivatives lower EVP in some species as a TM-independent mechanism to lower IOP.[71] During ROCK inhibitor clinical trials, up to 50% of patients demonstrated ocular surface vessel dilation.[67] Recent aqueous humor dynamic measurements under ROCK inhibitor treatment also showed statistically significant EVP reduction in humans.[72] Therefore, although undoubtedly impacting the TM, the suggestion has also been raised as to whether cytoskeletal relaxing agents also lower IOP through mechanisms outside or past the TM at aqueous and episcleral veins. It is here that SANS research supports these concepts because fluid shift altering VTCs lowered HDT-induced IOP elevation. Now, future innovation could be directed towards attempting to lower IOP by redistributing fluid balance in and around the eye.

CONCLUSIONS

Human exploration, for example during the early sea voyages, identified the previously unknown nutritional requirement of vitamin C to prevent scurvy. Here, long-duration spaceflight on the ISS has revealed SANS, a unique syndrome without an Earth-based correlate and therefore may offer new insights into the fields of vision science and ocular biology. Potentially involving several ocular anatomic compartments acutely or chronically (eg, the optic nerve, IOP, retina, blood flow, and refraction), a multidisciplinary approach is required to understand and mitigate SANS. Therefore, SANS represents a major astronaut safety hurdle for exploration-class space missions and further research will be needed to understand the pathophysiology, identify additional risk factors, create preventative countermeasures, and possibly develop treatments. NASA has funded several investigations that are ongoing or being implemented that use the chronic HDT model and 1-year spaceflight mission on the ISS. In addition, NASA has funded several ground and flight rodent experiments to obtain data that are difficult or impossible to obtain in human research studies. At this point, what is clear is that SANS is a unique disease entity and not the same as similar Earth-based optic neuropathies such as idiopathic intracranial hypertension. Further, research into SANS has the potential to yield new insights into Earth-based diseases such as glaucoma and various optic neuropathies.

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