# Evidence Report:

## *Risk of Spaceflight Associated Neuro-ocular Syndrome (SANS)*

## Human Research Program
## Human Health Countermeasures Element

Approved for Public Release: November 30, 2017

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**Table of Contents**

I.  **PRD RISK TITLE: RISK OF SPACEFLIGHT ASSOCIATED NEURO-OCULAR SYNDROME**

   A subset of astronauts develop neuro-ocular structural and functional changes during prolonged periods of spaceflight that may lead to additional neurologic and ocular consequences upon return to Earth.

II.  **EXECUTIVE SUMMARY**

   Over the last 40 years, reports of visual acuity impairments associated with spaceflight have been identified through testing and anecdotal reports. Until recently, these changes were thought to be transient, but a comparison of pre and postflight orbital MRIs, axial length measurements, and cycloplegic refraction measurements (some of which were performed 10 years after return from space) suggest a potential risk of permanent ocular changes largely as a result of globe flattening during spaceflight. The results of ocular testing show that a subset of crewmembers experience visual performance decrements and one or more of the following ocular findings: hyperopic shift, cotton-wool spots, choroidal folds, optic disc edema, optic nerve sheath distention, and posterior globe flattening with varying degrees of severity and permanence. These changes define Spaceflight Associated Neuro-ocular Syndrome (SANS). It is thought that the ocular structural and optic nerve changes are caused by events precipitated by the cephalad fluid shift crewmembers experience during long-duration spaceflight, and perhaps by additional spaceflight-related factors including the role of exercise or ambient $CO_2$ levels on the ISS. It is believed that some crewmembers are more susceptible to these changes because of their genetic/anatomical predisposition or lifestyle (fitness) related factors. Three important systems – ocular, cardiovascular, and central nervous – will be evaluated to understand the risk of developing SANS. Several hypotheses have been proposed to explain the visual acuity and structural changes that are associated with spaceflight; these hypotheses include increased intracranial pressure (ICP), localized cerebrospinal fluid (CSF) pressure elevation within the orbital optic nerve sheath as a result of compartmentalization, decreased venous compliance, and alterations in CSF dynamics. Few data exist from which to determine the extent or cause of SANS, and the knowledge gap related to etiology of the changes and the postflight resolution suggests that more monitoring is required before, during, and after spaceflight to characterize the risk. It will be important to determine the risk of developing SANS, predict whether severity of symptoms will greater during long-duration exploration-class missions, and establish any prolonged consequences upon return to Earth.

   It was initially thought that intracranial hypertension leads to SANS, and the opening pressure at lumbar puncture was measured in some crewmembers who had postflight optic disc edema. However, no crewmembers have reported the type of headaches typically associated with elevated ICP or demonstrated other neurological disturbances that often occur in patients with intracranial hypertension. Recent invasive measurements of ICP during parabolic flight suggest ICP may not be pathologically elevated during weightlessness. Rather, the inability to reduce ICP, as typically occurs when transitioning between supine and upright posture on Earth, may lead to chronic low-level elevation of ICP throughout spaceflight. To date, no preflight or in-flight invasive measures of ICP have been conducted on any astronaut.

An alternate theory proposes optic nerve (ON) sheath CSF pressure may rise as a result of compartmentalization within the orbit, and this could occur with or without a rise in ICP (Mader et al. 2011, 2015, 2016). In support of this theory, an astronaut who returned from long-duration spaceflight with unilateral grade 1 disc edema had a normal lumbar puncture opening pressure of 18 cm $H_2O$ 8 days after the mission (Mader et al. 2013). During spaceflight, this astronaut also had unilateral loss of previously visible spontaneous venous pulsations (SVPs) in the eye with the disc swelling, which continued to be absent 21 months after he returned to Earth, suggesting a long-term rise in sheath pressure (Mader et al. 2015). Another more recent study documented the case of an astronaut with optic disc edema and globe asymmetry 6 months after a long-duration spaceflight who had lumbar puncture opening pressures of 22 cm and 16 cm $H_2O$ at one week and one year post flight respectively (Mader et al. 2016). These lumbar puncture opening pressures are not believed to be high enough to cause or maintain disc edema. Thus, these findings suggest that increased ICP alone, at least in these astronauts, may not be the sole cause of the globe flattening or disc edema.

## III.    HRP RISKS AND GAPS

Below is a list of current knowledge gaps that will need to be closed to fully understand SANS and reduce the risk for exploration-class missions.

Current knowledge gaps:
- SANS1: What is the etiology of visual acuity and ocular structural and functional changes seen in-flight and postflight?
- SANS3: Identify in-flight diagnostic tools to measure changes in ocular structure and function and/or ICP related to the SANS.
- SANS12: What are the suitable ground-based analogs to study the SANS spaceflight-associated phenomenon?
- SANS13: What are the safe and effective countermeasures (CMs) to mitigate changes in ocular structure and function and intracranial hypertension for spaceflight?

## IV.    INTRODUCTION

As of 2016, 24 long-duration crewmembers had experienced in-flight and/or postflight visual acuity and ocular anatomical changes that included optic disc edema, globe flattening, choroidal folds, cotton wool spot, or hyperopic shifts. NASA has termed the risk of developing these symptoms and physiologic ocular changes during or after long-duration spaceflight as the Spaceflight Associated Neuro-ocular Syndrome (SANS) (previously this was termed Visual Impairment and Intracranial Pressure, VIIP). Initially, SANS incidence was classified using a Clinical Practice Guideline (CPG) score that grouped findings together. However, as our understanding of SANS has evolved, the medical, research, and occupational surveillance groups have moved away from the CPG classification system and now report crewmember incidence on the basis of each ocular finding. Figure 1 depicts this new representation of findings, including the number of crewmembers tested for each finding, which varies. Because the Medical Operations group has identified optic disc edema as the primary metric for SANS, the overall incidence of SANS is considered to be 16%. However, 24 crewmembers have been identified as having one or more of the constellation of symptoms, and because of the variability in the total

number of crewmembers tested for each finding, 38% to 51% of long-duration crewmembers have developed one or more findings associated with SANS.

After returning from a space mission, some crewmembers experienced transient ocular changes; whereas, for others these changes persisted with varying degrees of severity. While the underlying etiology of these changes is unknown at this time, the NASA medical community suspects that the microgravity-induced cephalad fluid shift and associated changes in physiology play a significant role in the development of SANS. The Human Health and Performance Directorate has assembled a SANS project team to address this issue using a comprehensive project plan that covers operations and research.

Though the clinical findings were important by themselves, the retrospective analysis of questionnaires given to 300 crewmembers who participated in long- or short-duration missions furthered our understanding of the phenomenon and indicated that these spaceflight-induced vision changes are not unique to long-duration fliers. Changes in visual acuity are not uncommon in astronauts, although there appears to be a higher prevalence among crewmembers who participate in long-duration missions. Specifically, 29% of crewmembers who participated in a short-duration Shuttle spaceflight and 60% of crewmembers who participated in long-duration spaceflight onboard the International Space Station (ISS) reported degradation of distance or near-visual acuity, which in some cases did not resolve in the years after a long duration ISS mission. Yet, only 9 of 47 astronauts (19%) tested following long-duration missions demonstrated refractive error changes ≥0.75D. In the initial 7 ISS astronaut case studies, which are presented below, preflight eye examinations were normal but most astronauts reported diminished visual acuity in flight that persisted after the mission.

## V.    SPACEFLIGHT AND ANALOG EVIDENCE

### A. Summary of Existing Spaceflight Data

#### 1. *Overview*

Alterations in visual acuity associated with spaceflight have been identified over the last 40 years by medical tests, research, and anecdotal reports. In 2011, the seminal report by Mader *et al.* (Mader et al. 2011) provided case studies of 7 ISS long-duration astronauts who underwent extensive postflight medical examinations in response to reports of changes in visual acuity. Of these 7 astronauts, 5 had disc edema, 5 had globe flattening, 6 had nerve fiber layer (NFL) thickening by optical coherence tomography (OCT), 7 had decrements in near vision, 5 had choroidal folds, and 3 had cotton-wool spots. Five of the 7 astronauts who reported altered near vision had hyperopic shift pre to post-mission that was equal to or greater than +0.50 diopters (D) spherical equivalent refraction in one or both eyes (range +0.50 D to +1.50 D). Five of the 7 had globe flattening that was identified by MRI. Lumbar punctures performed in 4 astronauts who had disc edema had opening pressures of 22, 21, 28, and 28.5 cm $H_2O$ performed at 60, 19, 12 and 57 days post-mission, respectively. A summary of findings from these crewmembers is presented in Appendix A.

Additional cases of altered visual acuity have been reported since, including an astronaut with a transient scotoma (visual field defect) who had to tilt his head 15 degrees to view instruments and read procedures.

To better characterize the signs and symptoms that have been related to SANS, Figure 1 shows the number of individuals who have presented with each sign and symptom of SANS, along with the total number of individuals that have been tested through Expedition 48. This chart does not capture whether an astronaut has developed signs on more than 1 spaceflight, in a single eye or both eyes, or whether differences in these variables exist between sexes. Because the Medical Operations group has identified optic disc edema as a finding that has the potential to be medically treated, optic disc edema has been used as the metric for quantifying SANS and indicates a prevalence of 16%. However, if the total number of subjects that have presented any of these findings are used to quantify the prevalence of SANS, the percentage of affected United States Orbital Segment (USOS) crewmembers (excludes Russian cosmonauts) ranges from 37.5% to 51%.
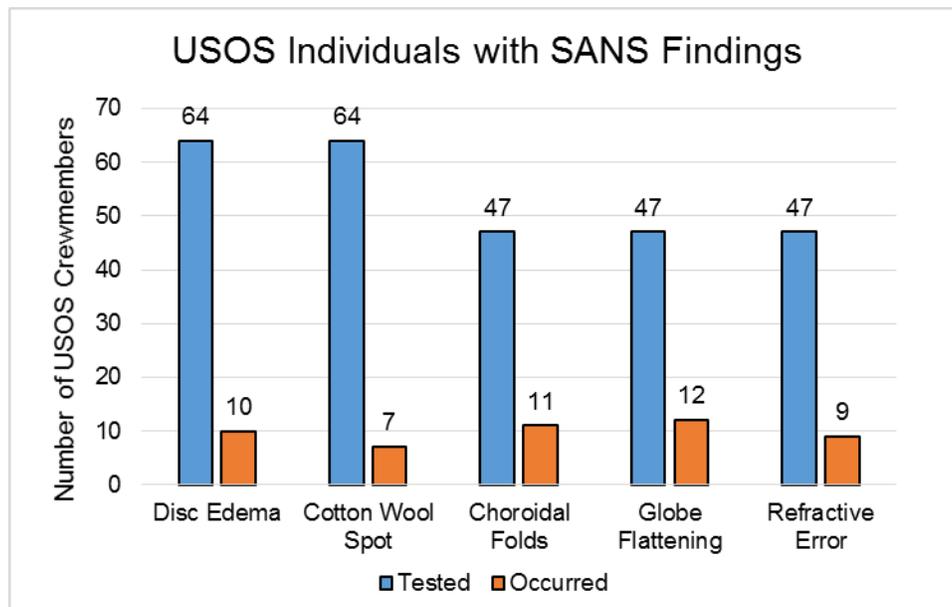


**Figure 1** *Total number of USOS individual crewmembers that have been tested (blue) and demonstrated presence of each SANS finding (orange) from Expedition 1-48. In total, 24 separate crewmembers demonstrated findings in one or more categories. Disc edema: Modified Frisen scale grade 1 or greater at first postflight eye exam (fundoscopy); Cotton wool spot: Observed during or after flight (fundoscopy); Choroidal folds: New or worsened relative to preflight (OCT); Globe flattening: A change relative to preflight (MRI or ultrasound); Refractive error: Change in cycloplegic (spherical) refraction ≥0.75D from before flight to first postflight eye exam. Courtesy of the Lifetime Surveillance of Astronaut Health.*

## 2. Seminal Report

The first U.S. case of vision changes observed during spaceflight was reported by an astronaut (C1) who noticed a marked decrease in near-visual acuity throughout his long-duration mission onboard the ISS but at no time reported headaches, transient visual obscurations, pulsatile tinnitus, or diplopia. His postflight fundus examination (Figure 2) revealed choroidal folds inferior to the optic disc and a single cotton-wool spot in the inferior arcade of the right eye. The acquired choroidal folds gradually improved but were still present 3 years after he returned from space. Intraocular pressure (IOP) measured by applanation revealed a 5 mmHg drop from before flight in both eyes. The left eye examination was normal. There was no

documented evidence of optic disc edema in either eye. Brain MRI, lumbar puncture, and OCT were not performed before or after flight on this astronaut.
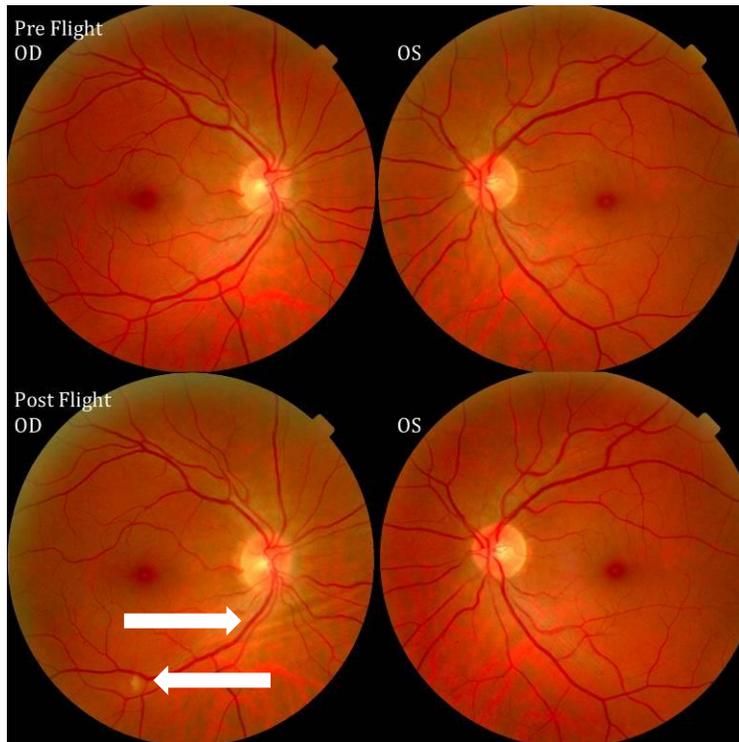


**Figure 2** *Fundus examination of first case of vision changes from long-duration spaceflight. Fundus examination revealed choroidal folds inferior to the optic disc (right-pointing arrow) and a single cotton-wool spot (left-pointing arrow) in the inferior arcade of the right eye.*

The second case of visual changes was reported approximately 3 months after launch when an ISS astronaut (C2) noticed that he could now only see the Earth clearly while looking through his reading glasses. This change persisted for the remainder of the mission without noticeable improvement or progression. The astronaut did not complain of transient visual obscurations, headaches, diplopia, pulsatile tinnitus, or visual changes during eye movement. Postflight fundoscopic images revealed choroidal folds and a cotton wool spot (Figure 3). In the years since the mission his vision has been stable with optical correction but has not returned to his pre-mission refractive status.

Fluorescein angiography confirmed the choroidal folds in astronaut C2. A magnetic resonance angiography (MRA) and magnetic resonance venogram (MRV) were normal. An OCT confirmed the increased retinal NFL thickening consistent with optic disc edema nasally and demonstrated a normal macula. A lumbar puncture, 2 months after astronaut C2 returned to Earth, documented an opening pressure of 22 cm $H_2O$ with normal CSF composition. The astronaut had additional postflight lumbar punctures with documented opening pressures of 26, 22, and 23 cm $H_2O$ at 17, 19, and 60 months, respectively. No improvement in visual acuity occurred during these 60 months.

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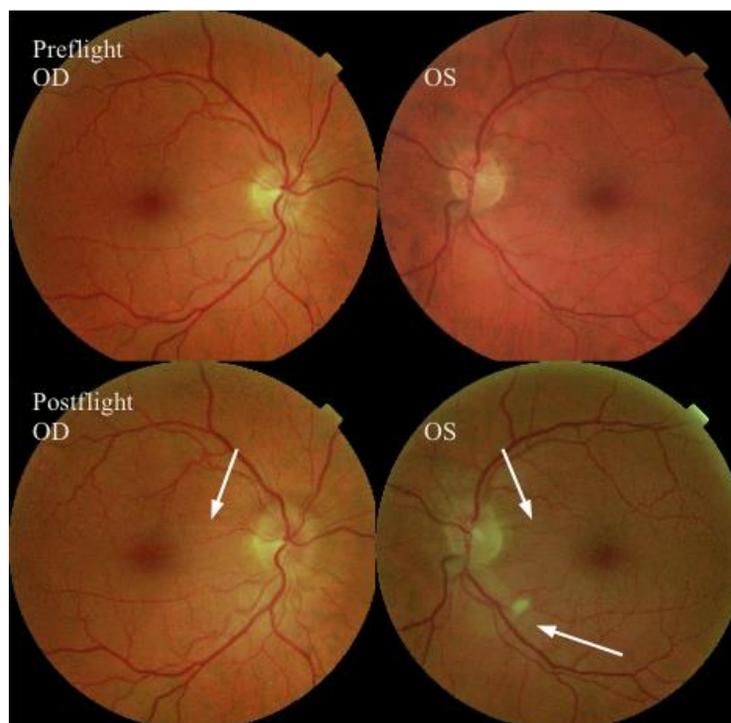
**Figure 3** *Fundus examination of the second individual who reported visual acuity and ocular changes related to long-duration spaceflight. Fundoscopic images showing choroidal folds (white arrows) in the papillomacular bundle area in the right eye and left eye and a cotton-wool spot (bottom arrow) at the inferior arcade in the left eye. Both optic discs show grade 1 disc edema.*

The third case of visual changes secondary to spaceflight onboard the ISS presented asymptomatically with no changes in visual acuity reported during the mission and no complaints of headaches, transient visual obscurations, diplopia, or pulsatile tinnitus. Upon return to Earth, no eye issues were reported by the astronaut (C3) at landing. Fundus examination of astronaut C3 revealed bilateral, asymmetrical disc edema (OD: grade 3 on the Frisén scale; OS: grade 1) (Figure 4). There was no evidence of choroidal folds or cotton-wool spots. A small hemorrhage was observed inferior to the optic disc in the right eye. Astronaut C3 had the most pronounced optic disc edema of all the astronauts reported to date, with a 0.5-D hyperopic shift in the right eye, and a 0.25-D hyperopic shift in the left eye. No choroidal folds, or globe flattening were noted. At 10 days post landing, an MRI of the brain and orbits showed a mild increase in CSF signal around the right optic nerve, but was otherwise normal. An MRV showed no evidence for cerebral venous sinus thrombosis. An OCT showed marked nerve fiber layer thickening consistent with optic disc edema and was thicker in the right eye than the left (Figure 5). A lumbar puncture performed 19 days after return to Earth documented an opening pressure of 21 cm $H_2O$ with normal CSF composition.
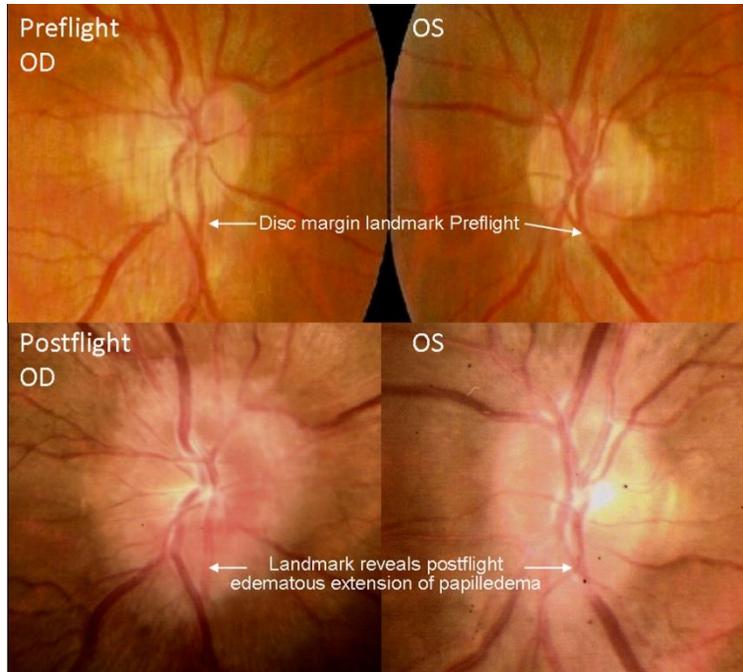
**Figure 4** *Fundoscopic images of the right and left optic disc of the third case showing profound grade 3 edema at the right optic disc and grade 1 edema at the left optic disc. Adapted from Mader TH et al. (2011) with permission from Elsevier, obtained via Copyright Clearance Center, Inc.*

The fourth case of visual changes on orbit was significant because the individual (C4) had previously undergone transsphenoidal hypophysectomy surgery for macroadenoma. Postoperative imaging showed no residual or recurrent disease. About 2 months into the ISS mission the astronaut noticed a progressive decrease in near-visual acuity in his right eye and a
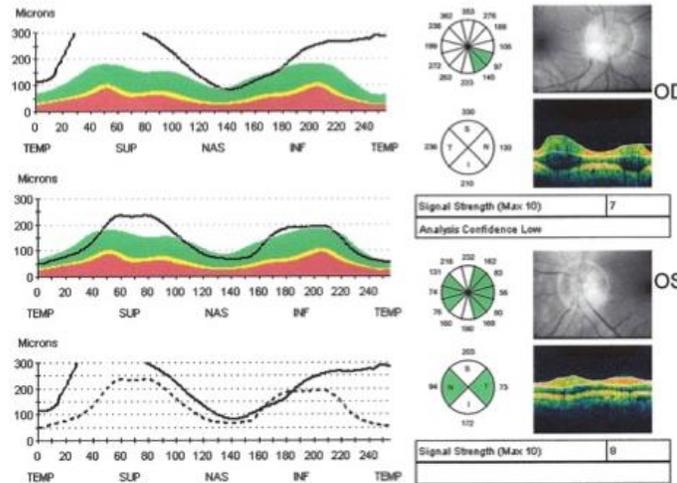


**Figure 5** *OCT examination of third case of visual changes from long-duration spaceflight. Postflight Zeiss Stratus OCT scans show significant NFL thickening (black line upper panel) consistent with the observed bilateral optic disc edema (OD>OS). Retinal Nerve Fiber Layer (RNFL) Thickness Profile – The black line indicates the thickness values of the patient's scan around the optic disc from temporal, superior, nasal, inferior to temporal (TSNIT). Colors indicate comparison versus normative database. Green: Within normal limits, with values inside the 95% normal range. Yellow: Borderline, with values outside 95% but within 99% confidence interval of the normal distribution (.01 < P < .05). Red: Outside normal limits, with values outside 99% confidence interval of the normal distribution.*

scotoma in his right temporal field of vision. He described the scotoma as fixed and translucent; he could not read 12-point font through the scotoma and he described it as the "shape of a football" held upright at arm's length. Astronaut C4 reported no transient visual obscurations, headaches, diplopia, pulsatile tinnitus, or vision changes during eye movement. During the mission the astronaut used a topical corticosteroid and oral ketoconazole for a facial rash, occasionally took vitamin D supplements, and took promethazine to treat symptoms of space adaptation syndrome. He had never used tetracycline or nalidixic acid. He participated in two extravehicular activities (EVAs or space walks) during the mission and was not exposed to any toxic fumes.

Preflight eye examination of astronaut C4 revealed a cycloplegic refraction of -0.75-0.50 × 100 on the right and plano -0.50 × 090 on the left, correctable in each eye to 20/15. He had a reading add of +2.00 OU. Ten days after he returned from space, astronaut C4 had a visual acuity that was correctable to 20/15 with a cycloplegic refraction of +0.75-0.50 × 105 on the right and to +0.75-0.75 × 090 on the left. He never experienced losses in subjective best-corrected acuity, color vision, or stereopsis. Fundus examination revealed mild, nasal disc edema (grade 1 Frisén scale) of the right eye with choroidal folds extending from the disc into the macula. Preflight to postflight IOP fell 4.0 mmHg OD, and 3 mmHg OS.

Three weeks into the same ISS mission as astronaut C4, another astronaut (C5) reported the fifth case of decreased near-visual acuity. Carbon dioxide ($CO_2$), cabin pressure, and oxygen ($O_2$) were reported to be within the allowable levels during all missions and none of the astronauts were exposed to any toxic fumes.

NASA consulted external experts to evaluate the data and the experts concluded that "the data seem to point to an eye/orbit-centered problem, and intracranial hypertension as the mechanism seems less likely, although it cannot be completely ruled out at this point in time." In-flight ocular ultrasound exams were performed on astronauts C4 and C5 to rule out increased optic nerve sheath diameter (ONSD), posterior globe flattening, detached retina, chorioretinopathy, or raised optic disc, and to confirm normal anterior eye anatomy. Ocular ultrasound was used because previous studies had validated the procedure and a nonexpert had successfully performed ultrasound examination of the eye onboard the ISS with guidance from ground support teams. The remotely guided ultrasound eye examinations of astronauts C4 and C5 demonstrated posterior flattening of the globe, dilated optic nerve sheaths, bilaterally distended jugular veins, and a raised right optic disc in the astronaut C4 (Figure 6 and Figure 7). Image files of a near and far acuity chart and an Amsler grid were uploaded and printed on orbit. Both astronauts reported decrements in near-visual acuity.
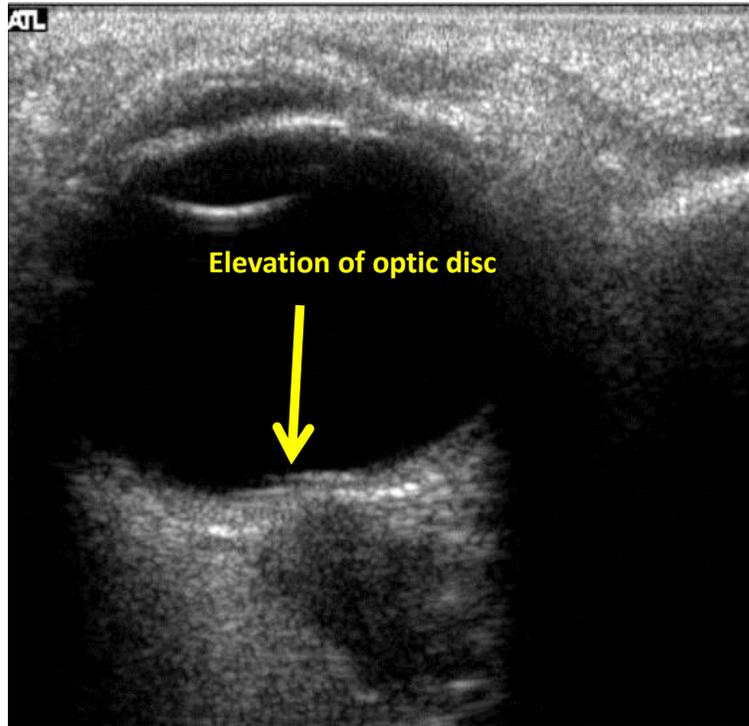
**Figure 6** *On-orbit ultrasound of posterior orbit of the fourth case of visual changes from long-duration spaceflight. In-flight ultrasound image of the right eye showing posterior globe flattening and a raised optic disc consistent with optic disc edema and raised ICP.*
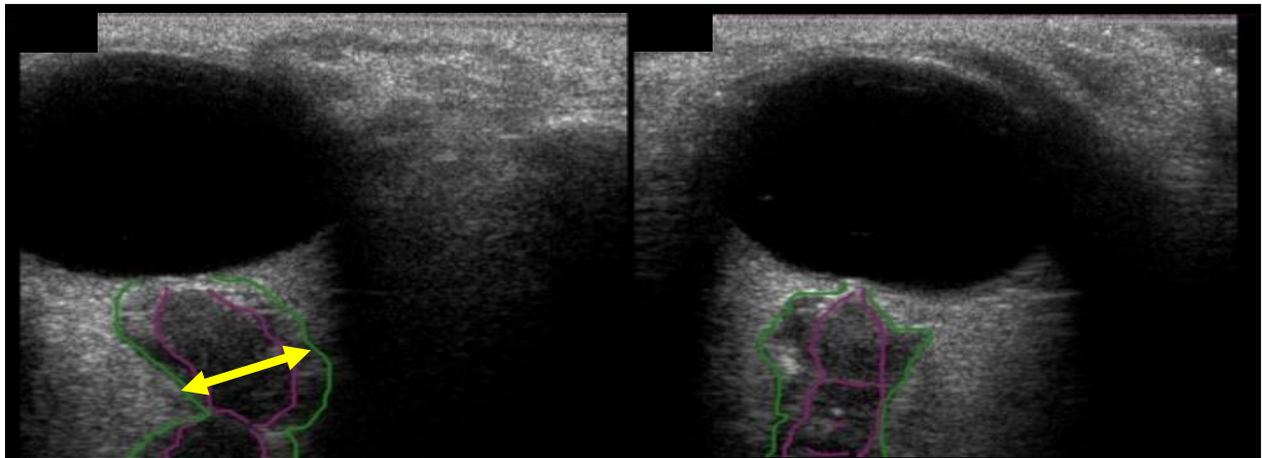


**Figure 7** *On-orbit ultrasound of optic nerves of the fourth case of visual changes from long-duration spaceflight. In-flight ultrasound shows proximal kinking and increased ONSD of approximately 12 mm that is consistent with raised ICPs. Optic nerve shown in purple and the ONSD in green.*

Three weeks after the ultrasound examination and Amlser grid testing, reading glasses (2.5 D and 3.25 D) were delivered to the ISS via the Space Shuttle and one astronaut reported that the 3.25 D glasses worked best. A video-ophthalmoscope system was also delivered to the ISS from the Shuttle, and remotely-guided dilated fundoscopic exams (Figure 8) were performed on both astronauts during their presleep period so that visual acuity loss from

Tropicamide drops would not impact other activities. The astronauts took turns being the operator and subject during these examinations and were given their preflight fundoscopic images to use as references. The fundoscopic video and captured images were downloaded from the ISS and sent to neuro-ophthalmological consultants who thought that the temporal location and shape of the reported scotoma in astronaut C4 was consistent with disc edema and an enlarged blind spot. The fundoscopic exam was normal for astronaut C5. Consultants agreed that no treatment was indicated at that time and that these images would serve as a baseline for follow up examinations throughout the rest of the mission. The inability to measure IOP on the ISS was also a factor in deferring any pharmacological interventions. Monthly remotely-guided ocular ultrasound, dilated video fundoscopic, and visual acuity exams were performed for the duration of the mission. These images allowed experts on the ground to make a diagnosis of mild optic disc edema in the right eye. Postflight fundus examination revealed mild, nasal optic disc edema (Frisen grade 1) of the right eye with choroidal folds extending from the disc into the macula. Postflight OCT confirmed optic disc edema and choroidal folds (Figure 8 and Figure 9).
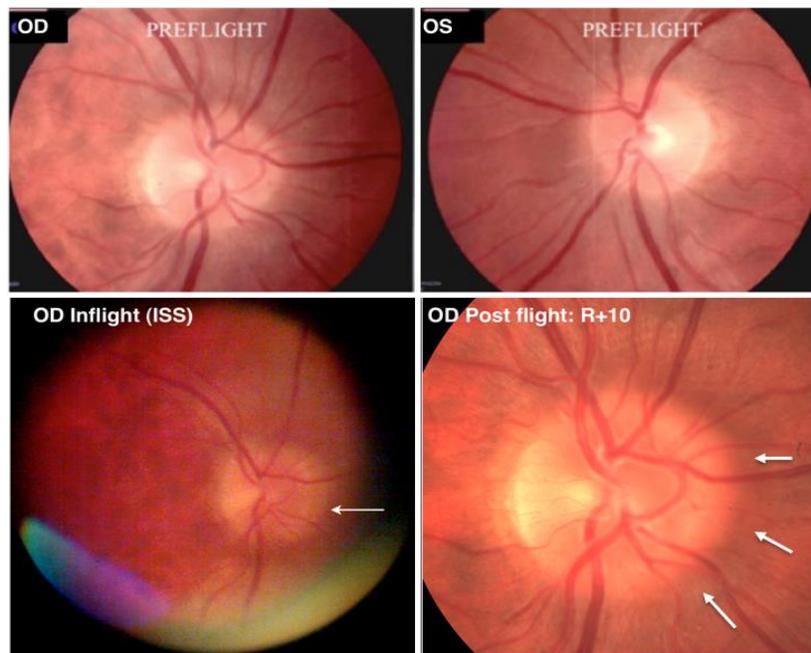


**Figure 8** *Fundus images from the ISS of astronaut C4 who had a case of visual changes resulting from long-duration spaceflight. (Top) Preflight optic nerve head photography. (Bottom left) In-flight (ISS) photography of the right optic disc obtained by remote guidance showing "C" halo associated with Grade 1 edema. (Bottom right) Postflight (R+10) image shows the "C" halo edema effect in greater detail with subtle nerve fiber glutting beyond the border of the edematous disc (arrows). Adapted from Mader TH et al. with permission from Elsevier, obtained via Copyright Clearance Center, Inc.*
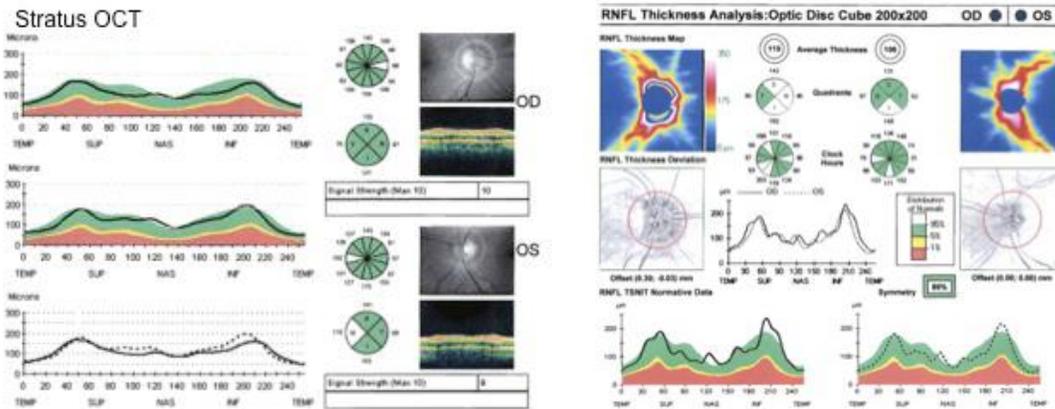
**Figure 9** *OCT of astronaut C4 who had vision changes resulting from long-duration spaceflight (right). Preflight Zeiss Stratus OCT showing the right and left NFL 'TSNIT' curve (left). Postflight Zeiss Cirrus OCT showing increased thickness of nerve fiber layer 'TSNIT' due to disc edema. Greater increase is noted in the right eye inferior sector consistent with postflight optic disc photography.*

Following their long-duration mission, astronaut C4 and C5 immediately returned to Johnson Space Center, allowing for 3-Tesla MRI images of the eye to be obtained within 3 days of landing. Previously, astronauts recovered in Star City, Russia for 21 days after landing and 3-Tesla MRI facilities were not available for these individuals. Because no preflight 3-Tesla head and orbit MRIs were collected on crewmembers C4 and C5, the standard 1.5-Tesla head MRI, MRA, and MRV obtained upon their selection into the ISS training flow (several years before mission assignment) were used to confirm that increased ONSD or posterior globe flattening were not present before the mission.

The MRI of the brain and orbits was repeated on astronaut C4 30 days after return from space, and documented bilateral, severely dilated optic nerve sheaths (right greater than left), bilateral flattening of the posterior globe (right greater than left), and thickened tortuous optic nerves (Figure 10, Figure 11, and Figure 12). However, flight surgeons have since reported that a brain MRI from astronaut C4, taken years prior to the spaceflight, showed similar optic nerve tortuosity, suggesting this finding existed in the astronaut before the mission. An intracranial MRV and MRA obtained from astronaut C4 showed no abnormalities, and a lumbar puncture, performed 57 days after return to Earth, documented an opening pressure of 28.5 cm $H_2O$ with normal CSF composition.
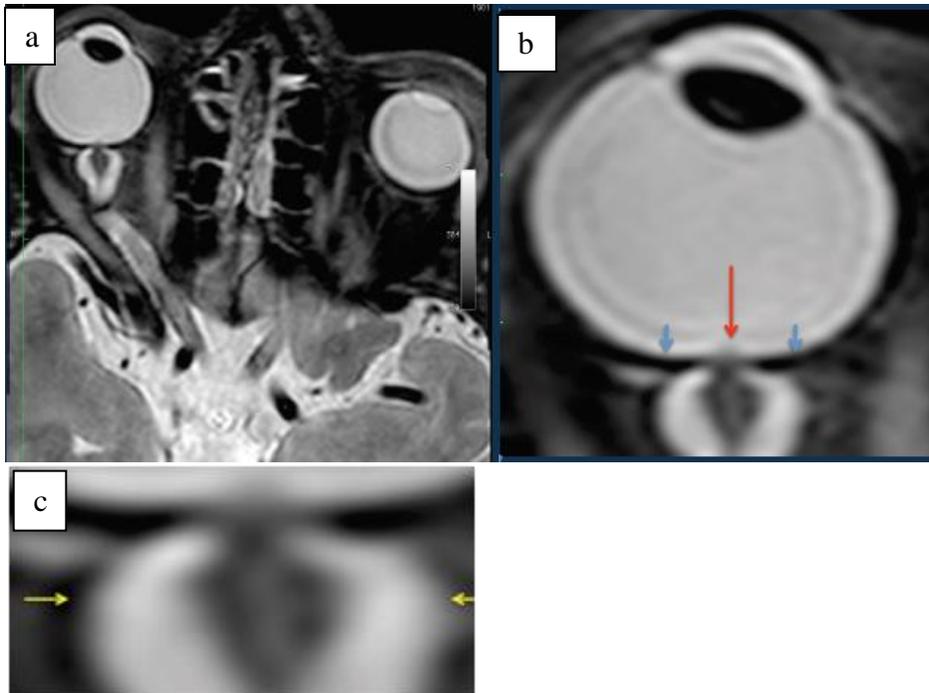
**Figure 10** *MRI (R+30 days) of the fourth case of vision changes resulting from long-duration spaceflight (a). Bilateral optic sheath dilatation remained. The right optic sheath diameter measures 10 to 11 mm (b and c); and the left optic sheath diameter measured 8 mm. These numbers are similar to the R+3 examination. Evidence of optic disc edema was seen on the right eye only. There was residual flattening of the posterior globes. The optic nerve remained thickened bilaterally measuring up to 5 mm on the right and 4 mm on the left. Bilateral tortuosity of the optic nerve sheaths also remained, with the kink at the optic nerve sheath approximately 1.1 cm behind the posterior margin of the globe. More recent discussions with flight surgeons indicate this tortuosity has been seen on MRI taken prior to the spaceflight. Red arrow depicts the optic disc edema, blue arrows show the flattened globe and the yellow arrows illustrate the distended optic nerve sheath. Reproduced from Mader TH et al. with permission from Elsevier, obtained via Copyright Clearance Center, Inc.*
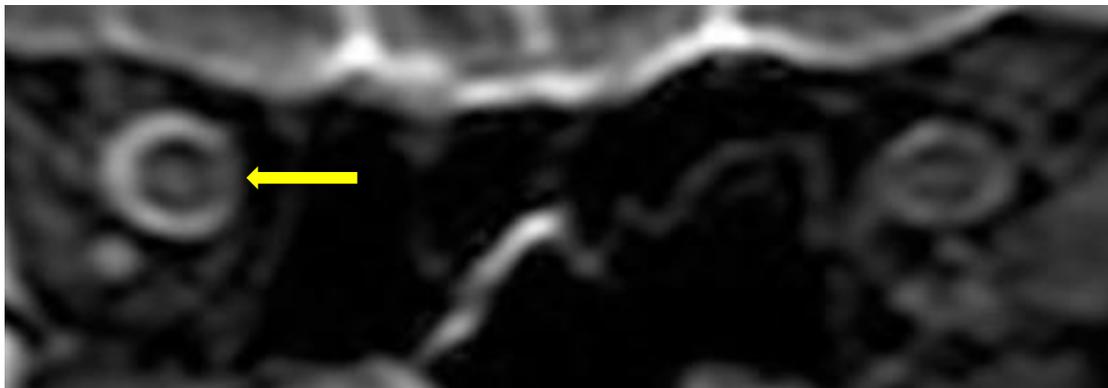


**Figure 11** *MRI (R+30 days) of the fourth case of vision changes resulting from long-duration spaceflight. There is prominence of central T2-hyperintensity of the optic nerves bilaterally, right greater than left approximately 10 to 12 mm posterior to the globe (arrow) that represents an element of optic nerve congestion.*
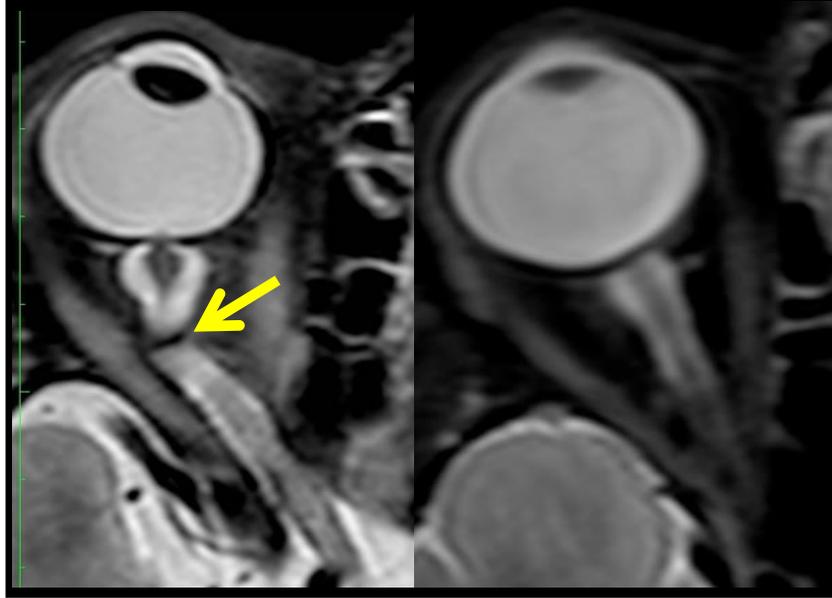
**Figure 12** *MRI (R+30 days) of the fourth case of vision changes resulting from long-duration spaceflight. Tortuous optic nerve and kink on left (arrow). MRI of opposite orbit on right.*

Astronaut C5 noticed vision changes 3 weeks into his ISS mission. This change continued for the remainder of the mission without noticeable improvement or progression. He never complained of headaches, transient visual obscurations, diplopia, pulsatile tinnitus, or other vision changes.

The preflight eye examination of astronaut C5 revealed a cycloplegic refraction of -5.75-1.25 × 010 on the right, and -5.00-1.50 × 180 on the left, correctable in each eye to 20/20 with a reading add of +1.75 OU. Dilated eye examination and fundus photos of astronaut C5 were normal. Upon return to Earth he noted the vision changes persisted. Postflight visual acuity was correctable to 20/20 OU with a manifest and cycloplegic refraction of -5.00-1.50 × 015 on the right and -4.75-1.75 × 170 on the left, and a reading add of +2.25 OU. He never experienced losses in subjective best-corrected acuity, color vision, or stereopsis. His fundus examination was normal with no evidence of disc edema or choroidal folds. However, an MRI of the brain and orbits, and ultrasound of the globes performed 3 and 8 days after landing respectively, revealed that astronaut C5 had bilateral posterior globe flattening, distended optic nerve sheaths, and tortuous optic nerves. OCT showed significant NFL thickening relative to preflight values and a normal macula (

Figure **13**). A lumbar puncture was not performed. This case is interesting because the astronaut did not have disc edema or choroidal folds but was documented to have NFL thickening, globe flattening, a hyperopic shift, and subjective complaints of loss of near vision.
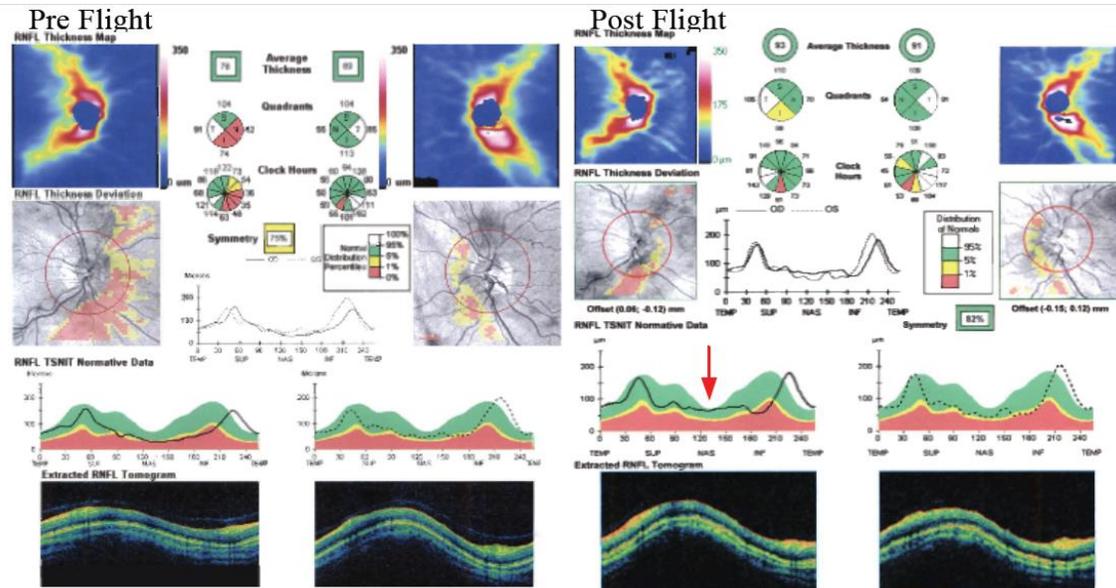
**Figure 13** *Preflight (left) and postflight (R+13 days, right) Zeiss Cirrus OCT of the fifth case of vision changes resulting from long-duration spaceflight showing right and left NFL 'TSNIT'. Postflight Zeiss Cirrus OCT shows increased thickness of the nasal (red arrow) NFL. Greater increase is noted in the right eye in the nasal quadrant NFL thickness; 42 μm preflight to 70 μm postflight. Fundus and optic disc imaging did not show presence of observable disc edema.*

The sixth case of vision changes was reported after the ISS astronaut (C6) returned from a 6-month mission; he noticed that his far vision was clearer through his reading glasses. A fundus examination performed 3 weeks postflight documented mild (grade 1) nasal optic disc edema in the right eye only. There was no evidence of disc edema in the left eye or choroidal folds in either eye (Figure 14). MRI of the brain and orbits, performed 46 days after return, revealed bilateral flattening of the posterior globe, right greater than left, and a mildly distended right optic nerve sheath. There was also evidence of optic disc edema in the right eye.

Fundus examination and OCT (Figure 15), performed 60 days postflight, documented that astronaut C6 had mild disc edema and a "new onset" cotton-wool spot in the left eye 2 disc diameters superior temporal to the disc, just inside the superior arcade. This cotton wool spot was not observed in the fundus photographs taken 3 weeks postflight.
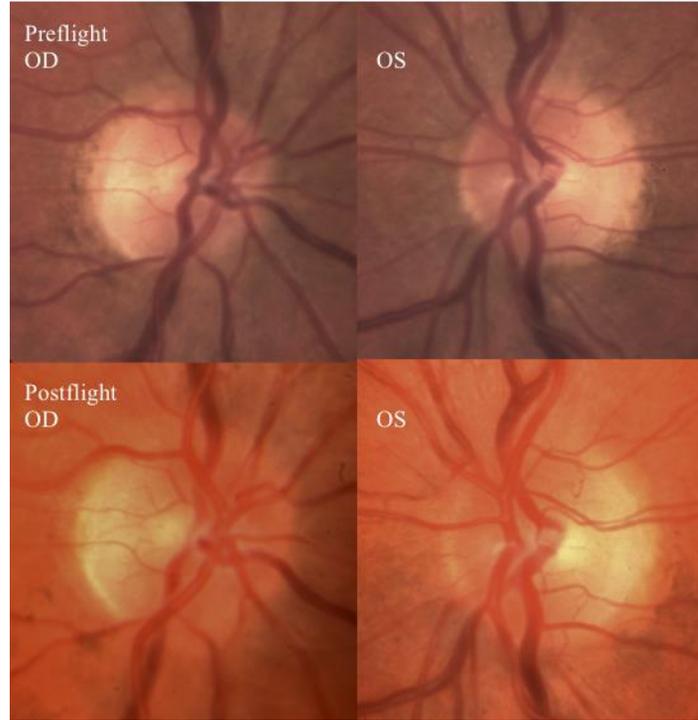
**Figure 14** *Fundus examination of the sixth astronaut who reported vision changes resulting from long-duration spaceflight. Preflight images of normal optic disc. Postflight right and left optic disc showed grade 1 (superior and nasal) edema at the right optic disc.*
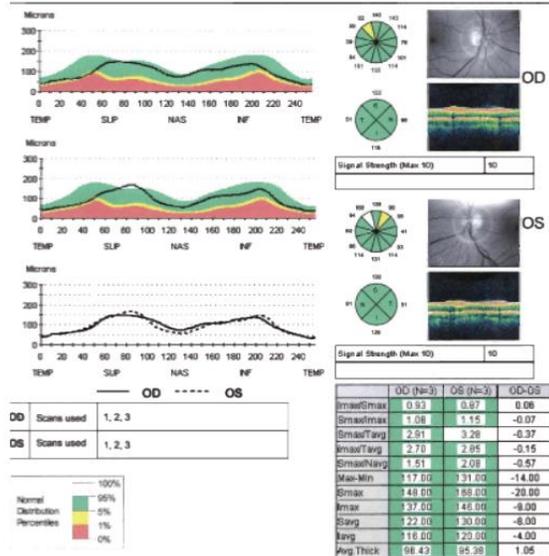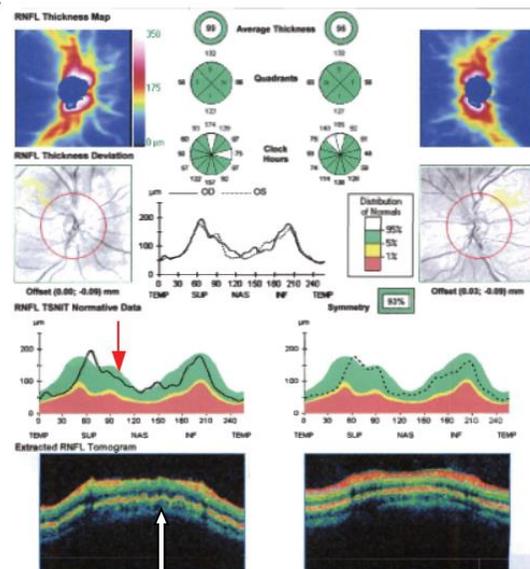


**Figure 15** *OCT of sixth case of vision changes resulting from long-duration spaceflight. Preflight Zeiss Stratus OCT showing the NFL 'TSNIT' curve. Postflight Zeiss Cirrus OCT showing a 50 µ increase in thickness (50% increase) of the nerve fiber layer at the superior and inferior poles (red arrow) consistent with changes seen in postflight optic nerve head photography. Choroidal folds are also visible (white arrow).*

The seventh case of vision changes associated with spaceflight is significant in that it was eventually treated postflight. Astronaut C7's preflight cycloplegic refraction was +1.25 sphere in both eyes and his fundus exam was normal. Approximately 2 months into the ISS mission astronaut C7 reported a progressive decrease in his near and far visual acuity in both eyes, which persisted for the remainder of the mission. Approximately 3 to 4 months into the 6-month mission he noticed that his normal "Earth" prescription progressive glasses were no longer strong enough for near tasks, at which time he began using his stronger "Space Anticipation Glasses" (+1.25 D greater). He never complained of transient visual obscurations, headaches, diplopia, pulsatile tinnitus, or vision changes during eye movement. The ISS cabin pressure, $CO_2$, and $O_2$ levels were normal during the mission (of note, the $CO_2$ levels on the ISS are nominally between 2.3 and 5.3 mmHg, equal to 10-20 times the normal terrestrial atmospheric level, which is 0.23 mmHg). Astronaut C7 was not exposed to any toxic substances. Three days after his return to Earth his visual acuity was correctable to 20/20 OU with a cycloplegic refraction of +2.75 sphere on the right, and +2.50 sphere on the left. He never experienced losses in subjective best-corrected acuity, color vision, or stereopsis. A fundus examination revealed that astronaut C7 had mild bilateral optic disc edema (grade 1), and choroidal folds (Figure 16 and Figure 17).
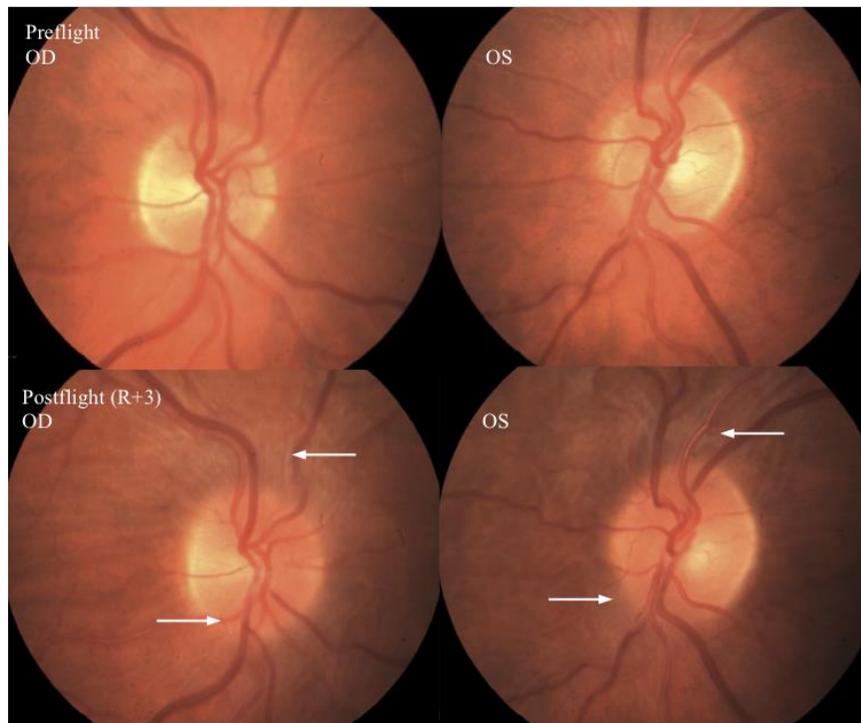


**Figure 16** *Preflight images of astronaut C7's right and left optic discs (upper). Postflight images of the ONH (lower) show more detail of the extent of the edematous optic disc margins and glutting of the superior and inferior nerve fiber layer axons and choroidal folds OD and OS (arrows).*

**Figure 17** R*ed-free fundus photography of astronaut C7 taken 30 days after return from an ISS mission highlighting the extent of the horizontal choroidal and retinal folds in the posterior fundus (OD>OS). Adapted from Mader TH et al. with permission from Elsevier, obtained via Copyright Clearance Center, Inc.*

An OCT confirmed that astronaut C7 had optic disc edema and choroidal folds. An MRI of the brain and orbits performed 6 days postflight documented bilateral flattening of the posterior globes, distended optic nerve sheaths and optic disc edema. A lumbar puncture, 12 days after return to Earth, documented an elevated opening pressure of 28 cm $H_2O$ with normal CSF composition.

Astronaut C7 was the only individual who was treated following a long duration spaceflight because by this time NASA Space Medicine had a developed treatment plan. The astronaut received acetazolamide (Diamox Sequel) 500 mg for 6 weeks, then 250 mg for another 2 weeks (total of 2 months). Over that time the lumbar puncture opening pressure decreased from 28 (pre-treatment) to 19 cm $H_2O$, and further treatment was deemed of questionable benefit. It is also noted that in this one case the individual's urinary creatinine rose from normal to 1.7, thus enhancing the desire to discontinue the medication.

The disc edema, posterior globe flattening, choroidal folds, and hyperopic shift seen in astronauts C2, C4, C6, and C7 appear consistent with findings of increased intracranial hypertension. Astronauts C2, C4, C6, and C7 presented with optic nerve sheath distention and posterior globe flattening as documented by MRIs taken 23, 30, 46, 6, and 7 days post-mission, respectively. Additionally, astronauts C4 and C7 had lumbar puncture opening pressures of 28.5 and 28 cm $H_2O$ at 57 days and 12 days, respectively after returning to Earth. CSF opening pressures were measured in astronaut C2 66 days after he returned from space and for astronaut C3 pressures were measured 19 days after return; pressures were not dramatically elevated, but they were above the upper range of normal of approximately 20 cm $H_2O$ for normal healthy individuals (Edsbagge et al. 2004; Berdahl et al. 2008a; b; Ren et al. 2010; Qvarlander et al. 2013; Petersen et al. 2016; Eklund et al. 2016; Lawley et al. 2017). While these values appear elevated compared to normal healthy populations, no astronaut has had a reference lumbar puncture before spaceflight to determine whether postflight values are elevated or values are actually normal for that individual. Furthermore, it is not known how a postflight ICP value compares to ICP values in weightlessness during long-duration spaceflight.

In summary, although a definitive etiology for these findings is unknown, it has been hypothesized that venous congestion in the brain and/or eye, brought about by cephalad fluid shifts and which may have exacerbated choroidal volume changes, may be a unifying pathologic mechanism. In light of the observations of vision change, optic disc edema, choroidal folds, and changes in the ocular ultrasound, head and orbit MRI, increased ICP, and fundoscopic image changes, NASA has initiated an enhanced occupational monitoring program for all active astronauts that includes enhanced attention to signs and symptoms related to ICP.

Interestingly, similar findings have previously been reported among Russian cosmonauts who flew long-duration missions on the Orbital Space Station Mir (the station was operational until 2001). The findings, published by Myasnikov and Stepanova in 2008 (Mayasnikov and Stepanova 2008), were part of a study that evaluated the retina by ophthalmoscopy, linear velocity of blood flow in the straight venous sinus of the brain by transcranial Doppler, and structural changes in the brain by MRI, under the premise that psychological difficulties reported during long-duration spaceflight could be caused by impaired in-flight cerebral hemodynamics. The study included 16 cosmonauts, of which 8 were found to have mild to moderate optic disc edema on landing day, corresponding to NASA's CPG class 3 and 4. In addition to optic disc edema, transcranial Doppler confirmed elevation of linear velocity of blood flow in the straight venous sinus of the brain in 9 of 13 crewmembers who underwent Doppler testing; flow velocities ranged from 30 to 47 cm/sec (normal range 14-28 cm/sec). MRI of the brain was obtained from 10 of the crewmembers, and 1 crewmember exhibited "signs of moderate intracranial hypertension" although the signs themselves are not described. This crewmember had congenital low-lying cerebellar tonsils, which were thought to have impeded CSF outflow from the cranium into the spinal canal. A second MRI obtained from this individual 3 months postflight reported resolution of the signs of intracranial hypertension. Of note, the spaceflight environment of the Mir was very similar to that of the ISS, including exposure to both microgravity and high levels of $CO_2$.

*3. Case reports*

One of the original 7 crewmembers reported by Mader (Mader et al. 2011) completed a second long-duration spaceflight 9 years later. During his initial flight he developed choroidal folds and a single cotton wool spot in the right eye; during his second flight there was a recurrence of more widespread choroidal folds and he presented with optic disc edema, which was also in the right eye (Mader et al. 2013). This crewmember's near-visual acuity in-flight was not different from preflight, and postflight cycloplegic refraction did not change after the second flight. Postflight OCT imaging revealed thickening of the RNFL in the right, but not the left eye. Clinical impression of the MRI revealed bilateral globe flattening. Fundus and OCT imaging taken 52 days following the second flight documented a normal optic disc in both eyes and normal RNFL thickness. The authors of this case report speculated that ocular effects resulting from spaceflight may be cumulative and the changes that developed during the first mission may have predisposed this astronaut to additional ocular changes during the next spaceflight.

A follow-up *Letter to the Editor* described unilateral loss of SVPs in this same astronaut following his second mission (Mader et al. 2015). Prior to the second mission SVPs were present bilaterally on ophthalmoscope inspection, but were no longer present in the fundoscopy video obtained in the right eye, in which optic disc swelling was present, 5 months into the spaceflight mission. SVPs remained prominent in the left eye and the fundus was normal. A postflight MRI

obtained 6 days after return from space revealed bilateral globe flattening, and a repeat MRI showed that this flattening was still present 7 months later. The opening pressure of a lumbar puncture performed 8 days after landing was 18 cm $H_2O$. By 52 days after return from space the optic disc swelling in the right eye had resolved, yet 21 months after the mission SVPs remained absent and choroidal folds persisted in the right eye.

A more recent report describes an ISS crewmember (C8) who presented with asymmetric optic disc swelling, globe flattening, and choroidal folds (Mader et al. 2017). Optical coherence tomography 90 days into the mission suggested optic disc edema and choroidal folds were present in the right eye, with only minimal swelling and a normal optic disc in the left eye. Mild optic disc swelling and moderate choroidal folds persisted in the right eye 4 days after this individual returned to Earth and were still visible on retinal photography 90 days after landing. Lumbar puncture performed 7 days and 1 year after landing recorded opening pressures of 22 cm $H_2O$ and 16 cm $H_2O$, respectively. Twenty-two months after landing the visual field was normal.

While the reports of optic disc edema and globe flattening presented in the seminal paper (Mader et al. 2011) led to the hypothesis of a pathology resulting from elevated ICP, authors of this more recent case study suggest this cause is less likely for a number of reasons. The postflight lumbar puncture opening pressures suggest that ICP was not high enough to result in optic disc edema. More than 90% of terrestrial patients with idiopathic intracranial hypertension report severe headache and most present with bilateral optic disc edema, yet astronaut C8 only reported occasional mild headaches and had asymmetric unilateral optic disc swelling. An alternative mechanism resulting from compartmentalization and sequestration of cerebral spinal fluid in the orbital subarachnoid space was proposed. This hypothesis points to alterations in CSF absorption within the orbit due to impaired venous and lymphatic drainage in weightlessness, leading to a locally elevated pressure within the optic nerve sheath and the possible accumulation of toxic substances.

The majority of the medical data published on SANS stems from data collected on U.S. astronauts and NASA's partner agencies (European Space Agency, Canadian Space Agency, and Japan Aerospace Exploration Agency); however, Russian cosmonauts have also spent a significant amount of time in weightlessness, yet they have not reported similar symptoms of SANS. A recent editorial (Bogomolov et al. 2015) suggested that Russian countermeasures including lower-body negative pressure (Chibis device) may provide them protection that astronauts from other agencies do not have. The Russian authors reported no significant deterioration of visual function in any Russian cosmonauts returning from missions that lasted up to 437 days on the Salyut or Mir space station. Furthermore, they reported that none of the cosmonauts showed optic disc edema (based on ophthalmoscopy) during the postflight period, yet they also stated that a slight or transient peripapillary edema developed during the first 3-4 days of rehabilitation on Earth. This edema was also seen in cosmonauts after they returned from short-duration spaceflights. The authors suggested this transient edema resulted from transversely-loaded G-forces upon re-entry aboard the Soyuz spacecraft. Whether Russian cosmonauts are truly protected from developing SANS remains unconfirmed. Some Russian crewmembers have volunteered to participate in NASA research experiments and this may begin to provide the first in-flight evidence that may help elucidate whether Russian cosmonauts truly are protected from SANS.

4. *Intracranial Pressure (ICP) in a Macaque Monkey During Spaceflight*

In 1994 a Russian publication provided evidence of ICP measurements during short-duration spaceflight in a Macaque monkey named Krosh on the biosatellite Cosmos-2229 (Krotov et al. 1994). A surgically implanted pressure sensor was placed in contact with the dura mater 25-30 days before launch. ICP was measured during seven 5-minute sessions throughout the 20 hours before launch, continuously for 2 hours starting 21 minutes after entering weightlessness, and then for 5 minutes every 2 hours throughout the duration of the flight. Before launch, while in the rocket on the launch pad, ICP in the "physical mid-position" (head and legs at the same level) averaged $10.23 \pm 0.12$ mmHg (range: $8.5 - 12.1$ mmHg). During the final 2 hours before flight the average ICP was $11.66 \pm 0.09$ mmHg. Twenty-two minutes after entering weightlessness ICP was 13.78 mmHg and continued to increase to ~15 mmHg over the first few hours. By flight days 3 to 5 ICP reached an average of 14 mmHg, driven in large part by increased ICP during the night. Conversely, from flight days 6 to 9 ICP was higher during the day than at night and the average ICP returned to values that were similar to preflight baseline. Disruption in the sleep-wake cycle throughout the mission led to the changes in the circadian pressure rhythm such that ICP was higher at night than during the day on flight day 8 and 9. The ICP pulse also demonstrated changes during weightlessness, with a decrease in amplitude of the arterial component and an increase in amplitude of the venous component. This also tended to return toward preflight morphology during flight days 5 to 9. In comparison to the 4 mmHg change in ICP observed from preflight to weightlessness, posture changes on Earth (moving the monkey from upright to supine) increased ICP by 10 mmHg.

5. *Medical Operations Testing*

NASA's Space and Clinical Operations Division, in collaboration with the SANS project, has implemented an expanded set of medical tests before, during and after spaceflight to determine the existence and degree of alterations in the structure and function of the eye. The tests relating to eye health are captured in the Medical Requirements Integration Document (MRID) in section MedB 1.10 ("MedB 1.10 Pre and Postflight Physical", rev 3.4, 2016). The suite of tests provides information on eye and brain health for flight qualification prior to a mission, aids in monitoring astronauts for the development of SANS-related signs and symptoms during flight, and allows monitoring of recovery after flight.

A 3-Tesla MRI of the brain and orbits is performed 21 to 18 months before a mission, and within the first three days of returning from space. The brain anatomy is evaluated against standard clinical criteria for the presence of abnormalities in the white and grey matter, CSF spaces, and vasculature. Attention is paid to signs of elevated ICP such as enlarged ventricles, compression of the pituitary gland, or changes in the configuration of the sella turcica. Orbital images are assessed for optic nerve sheath diameter, optic disc elevation, globe flattening, and optic nerve tortuosity − all findings that may indicate the onset of SANS. If any of the above signs of elevated intracranial or ON sheath pressure are documented, the MRI is repeated as clinically indicated.

Ocular ultrasound is conducted 9 to 6 months before flight, in-flight, and during the first 3 days postflight to document globe flattening, ONSD distension, and optic nerve sheath

tortuosity. Subjects are supine during ground testing. During flight, measurements are made on flight days 30 and 90, and on R-30 (30 days before returning to Earth). In-flight sessions are remotely guided by sonographers in mission control via real-time cabin video and ultrasound feed from the ISS. The astronauts onboard the ISS acquire the images on one another while receiving expert guidance from mission control.

Vision testing is performed 21 to 9 months before launch and again 6 to 9 months prior to launch. In the postflight period, testing is completed during the first three days upon return to Earth and as clinically indicated. The ground portion of vision testing consists of the following:

- Vision questionnaire
- Visual acuity (distance and near)
- Refraction (manifest and cycloplegic)
- Amsler grid
- Contrast sensitivity
- Pupil reflexes
- Extraocular muscle balance
- Biomicroscopy (slit lamp)
- Dilated fundus examination
- Applanation tonometry (Goldmann, Tonopen)
- Optical coherence tomography (high resolution)
- Threshold automated visual fields
- High resolution retinal photography
- Optical biometry (axial length)
- Magnetic resonance imaging (brain and orbits)

During flight, far visual acuity is tested for each eye with and without a corrective lens using a software application loaded onto the OCT laptop that provides a screen shot of a standard logMAR Snellen chart. The astronaut is positioned 15 feet away from the OCT laptop and ground-support personnel control the software application by remotely accessing the OCT laptop. The software is also used for Amsler grid testing during each session for both the right and left eyes. Any changes to the appearance of the grid (wavy, blurred, or missing lines) indicate a positive for this test. Near visual acuity is tested for each eye with and without a corrective lens using a paper-based eye chart located 16 inches from the astronaut on the wall of the laboratory module of the ISS. Laptop-based contrast sensitivity testing is not routinely performed during flight, but is available for "as clinically indicated" situations.

OCT is a diagnostic imaging technique that is based on analysis of the reflection of low-coherence infrared light from the tissue under examination. It involves measurements of retinal thickness, volume, and retinal nerve fiber layer (RNFL) thickness using a method of quantitative cross sectional analysis. OCT is conducted before, during, and after spaceflight to identify and detect changes in key posterior ocular areas, especially the optic disc, retinal nerve fiber layer (RNFL), retinal pigment epithelium (RPE), and the vascular choroid. The OCT scans are performed with the subject placing their chin on a chin rest while the device performs a scan of the eyes.

Dilated fundoscopy is performed on the right and left eye to obtain images of the retinal surface and optic disc. All in-flight exams are remotely guided using the current fundoscope and desktop streaming software technology. Still images and short video clips are recorded and downlinked.

The in-flight vision questionnaire asks if the crewmember has noticed any change in his or her vision since launch or the last in-flight exam. Respondents rate any change as mild (does not affect daily activities), moderate (crewmember had to make changes to accommodate, but completion of all activities was achieved), or severe (changes significantly affected or interfered with completion of daily activities). The vision change questionnaire includes questions about distortion, vision in dim light, fluctuation in visual acuity, depth perception, double vision, transient vision loss, and change in near, intermediate, and distance vision. Additional questions include type of eyewear used, i.e., progressive lenses, bifocal lenses, reading glasses or adjustable eyewear. The crewmember is also asked is they have any of the following symptoms: headaches, tinnitus, nausea, or impairment in cognition. If present, he or she is asked to rate the intensity as mild, moderate, or severe.

Refractive error is a measurement of the lens power needed to correctly focus light on the retina of the eye. Two types of refraction tests, manifest and cycloplegic, are used to measure refractive error. In manifest refraction, refractive errors are measured while the eyes own crystalline lens is able to accommodate. During manifest refraction, subjects may "over-use" their accommodative ability while trying to read a line of letters. This must be controlled to properly determine the refractive error and prescribe the appropriate correction. Cycloplegic refraction determines the total refractive error while the muscles that aid in focusing the eye are temporarily paralyzed. Cycloplegic eye drops are used to temporarily relax the cilliary body, the focusing muscle of the lens.

Standard automated visual field testing (Zeiss Humphrey SITA standard) is conducted on astronauts before and after their spaceflight missions to screen for changes in central and peripheral vision. Humphrey's automated static threshold visual field is used to simultaneously test different locations throughout the visual field. A SITA standard 30-2 is used to test the central 30 degrees of the visual field by displaying a dim light at a particular location. If the astronaut does not see the light, it is gradually made brighter until it is seen. The minimum brightness required for the detection of a light stimulus is the "threshold" sensitivity level for that location. This procedure is then repeated at several other locations until the entire visual field is tested. The 30 degree test is used to assess 76 individual points that are separated by 6 degrees.

Additional testing conducted pre- and postflight includes pupillary reflexes, extraocular muscle balance, biomicroscopy, and optical biometry. Retinal photography is conducted before, during, and after the mission.

## 6. *Optic Nerve Sheath Diameter (ONSD)*

Since the initial hypothesis suggested that elevated ICP was a precipitating factor in the development of changes to the structure and function of the eye, NASA's Medical Operations group used ultrasound imaging of the optic nerve and optic nerve sheath in an attempt to noninvasively assess and longitudinally track signs of elevated ICP. With increasing ICP, the

local compartment of the CSF, predominantly in the retrobulbar portion of the optic nerve, is distended by hydrostatic transmittance of CSF pressure within the subarachnoid space (SAS). As noted above, it is also possible that the increase in optic nerve sheath pressure and resultant distension may occur as a localized compartment syndrome even in the presence of non-elevated ICP. This can result in an increase in the local ONSD, even before edema appears at the optic disc, which may reflect the accommodative capacity of the retrobulbar space. Although a number of studies have demonstrated a relationship between ONSD and ICP, a large range of ICP values are required to achieve statistically significant correlations. Because ultrasound assesses ONSD noninvasively, ONSD measurements are conducted pre-, in-, and postflight to track any changes immediately posterior to the globe; pre- and postflight analysis of MRI data also provide assessment of ONSD.

MRI data collected from 27 astronauts after they returned from long-duration spaceflight was used to measure ONSD; 8 of these individuals subsequently flew a second short-duration mission and had a second MRI available for review (Kramer et al. 2012). The ONSD of the 8 subjects did not change after their short-duration spaceflight relative to their ONSD after a previous long-duration mission. After long-duration spaceflight, 20 astronauts who did not present with globe flattening had an average ONSD of $5.8 \pm 0.6$ mmHg, while 7 astronauts with globe flattening had an ONSD of $7.2 \pm 1.5$ mmHg. When grouped by presence of nerve kinking, those with nerve kinking (n=4) had a greater ONSD than those without (n=23) ($7.5 \pm 1.1$ vs. $5.9 \pm 0.8$ mmHg, respectively).

## 7. Intraocular Pressure

In light of the relationship between IOP, glaucoma, and RNFL pathology, assessment and longitudinal tracking of IOP during prolonged spaceflight was also a priority for the Medical Operations group. Preliminary data have shown that IOP is elevated above ground-based values upon initial exposure to weightlessness (Draeger et al. 1995). Because there are no valves in the veins in the eye or the brain, there is no venous pump, as there is in the legs, to facilitate blood return to the heart. Thus, in weightlessness, where no venous pump or gravity exist, blood flow may stagnate and accumulate in the veins, contributing to the distended facial and neck veins noted in astronauts. In addition, a cephalad redistribution of fluids is known to occur with exposure to weightlessness, which has been recorded as changes in leg girth, facial edema, and verbal reports of head fullness and nasal congestion. Venous engorgement elevates the cerebral post-capillary venous pressure. This rise in venous pressure affects the episcleral veins as well as the choroid space within the eye. Congestion in the venous system will cause a concomitant rise in pressure in the episcleral vessels of the eye and will increase the resistance to aqueous-humor outflow, leading to a rise in IOP (Mader et al. 1993). However, the aqueous-humor outflow system is slow and would not account for the sudden spike in IOP documented in head-down and parabolic flight studies. Therefore, sudden choroidal expansion within the eye is a more likely explanation for the rise in IOP. Since the choroid is drained by the vortex vein system and lacks autoregulation, a sudden rise in venous pressure from cephalad fluid shifts could inhibit choroidal drainage causing sudden choroidal expansion and a concomitant IOP spike. Indeed, modeling work suggests ocular hemodynamics governs the response of IOP to acute gravitational changes (Nelson et al. 2017).

Draeger (Draeger et al. 1995) reported an initial 20% to 25% increase in IOP 44 minutes

into a Space Shuttle flight that was measured using a hand-held applanation tonometer. In a subsequent experiment, IOP in 2 cosmonauts onboard a Soyuz vehicle bound for the Mir Space Station increased 92% 16 minutes after reaching weightlessness (Draeger et al. 1993). In a follow-up 6-day experiment onboard STS-55 (the German D2 mission) diurnal IOP was recorded and a 114% increase in IOP was noted 16 minutes after crewmembers reached microgravity (Draeger et al. 1994).

Tonometry data collected as part of the medical testing requirements uses the gold standard Goldman applanation tonometry pre- and postflight on subjects while seated, and the handheld Tonopen is used by crewmembers on each other during spaceflight. Preliminary data supplied by the Lifetime Surveillance of Astronaut Health for 15 subjects suggest there is no change in IOP for the group as a whole on flight day 30 and 30 days prior to return to Earth (R-30) compared to pre- or postflight (Figure 18). The subjects who demonstrated optic disc edema on fundoscopy (red symbols) upon return to Earth do not appear different from the remaining 13 crewmembers (Figure 19).
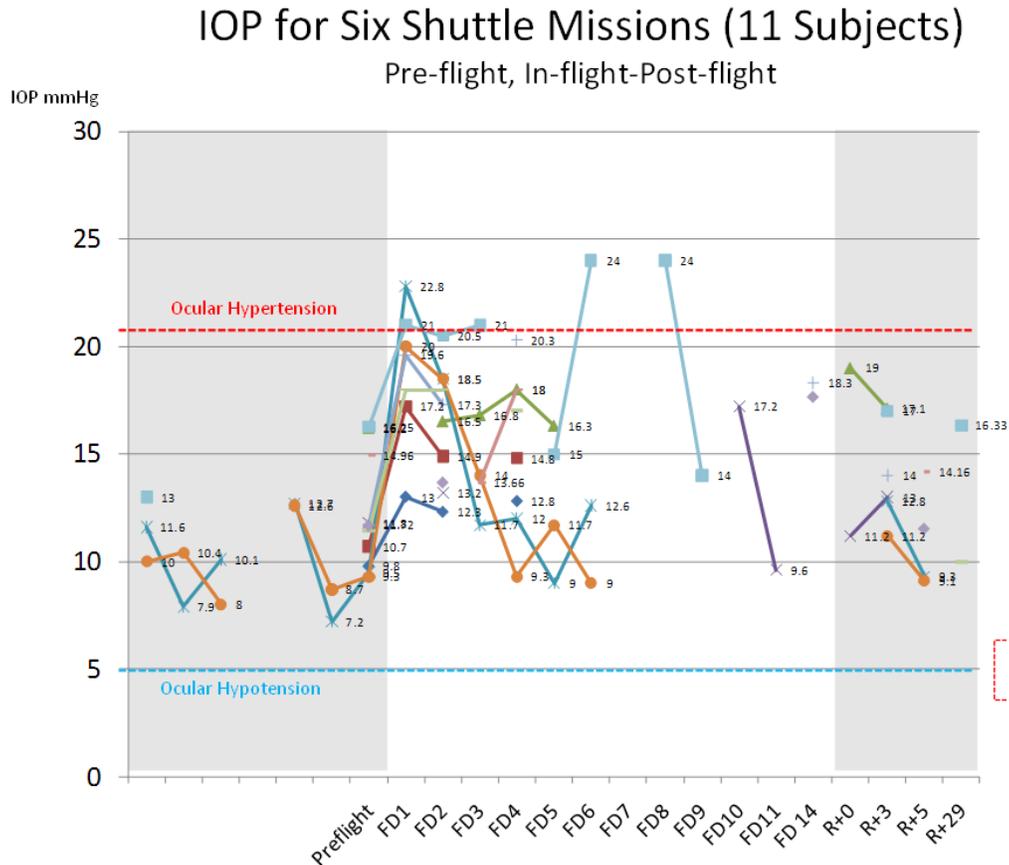


**Figure 18** *IOP values for eleven subjects before, during (non-shaded region), and after six Shuttle missions. FD= flight day*
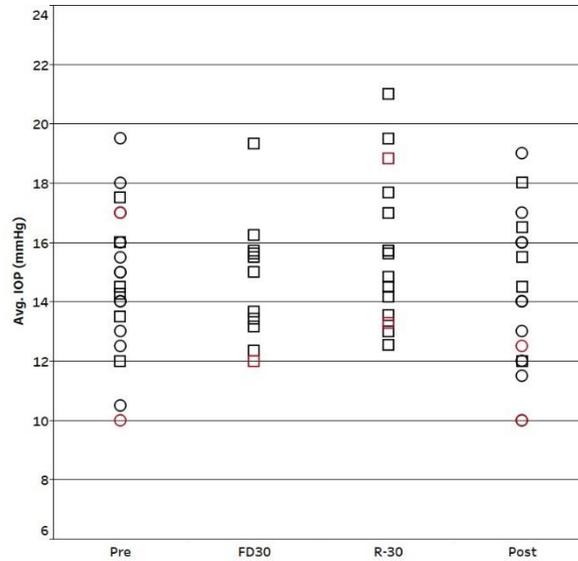
**Figure 19** *Intraocular pressure averaged between right and left eyes collected with Goldman Applanation tonometry (circles) or Tonopen (squares). Red symbols (n=2) are subjects who demonstrated optic disc edema in one or both eyes during postflight fundoscopy exam. Black symbols (n=13) are subjects without signs of optic disc edema. Pre, preflight; FD30, flight day 30; R-30, 30 days prior to return; Post, postflight. Provided by NASA Lifetime Surveillance of Astronaut Health.*

## 8. *Magnetic Resonance Imaging*

MRI of the eye is acquired before and after long-duration space missions as part of the astronauts' medical monitoring. In 2012 Kramer *et al.* reported the prevalence of globe flattening and ONSD distension after short- and long-duration spaceflight as measured by MRI, and the authors suggested these findings were similar to terrestrial IIH patients (Kramer et al. 2012). Although limitations exist in translating postflight findings into speculation about occurrences during spaceflight, quantification of CSF flow dynamics may provide insight into changes in ICP during spaceflight. In dogs, experimentally induced intracranial hypertension above 27.2 cm $H_2O$ results in down-regulation of CSF production (Miller et al. 1986). This led to the hypothesis that the combination of a headward fluid shift, intracranial volume expansion, and resulting modulation of CSF hydrodynamics may occur in astronauts during prolonged weightlessness. Kramer, *et al.* (Kramer et al. 2015) graded the degree of globe flattening from pre- and postflight MRIs obtained from 14 astronauts (7 long-duration fliers and 7 short-duration fliers), 13 of whom had previous spaceflight exposure. Two astronauts (one short- and one long-duration flier) had optic disc protrusion after their mission, and there was an increased incidence and severity of globe flattening in the long- (n=4) vs short-duration (n=2) fliers. Postflight CSF production rate was significantly higher postflight than preflight in the subgroup who had globe flattening, whereas CSF production rate was not significantly changed for the group that did not have globe flattening; no reports were provided for the effect of flight duration on CSF production rate. Conversely, astronauts that did not have globe flattening had a significant increase in CSF maximum systolic velocity, and those with globe flattening did not. These results suggest that spaceflight induces a down regulation of CSF production in response to the cephalad fluid shift. Upon return to the 1*g* environment on Earth the reversal of the cephalad fluid shift causes a drop in ICP and a compensatory upregulation of CSF production. Kramer *et al.* further speculate that the CSF maximum systolic velocity represents a marker of compensatory reserve and increased

30

craniospinal compliance. If the astronauts with greater CSF maximum systolic velocity had anatomical differences in their spinal canal, thecal sac, or compression of the epidural venous plexus that allowed them to maintain a greater capacity to blunt increases in ICP, this could explain why they did not develop globe flattening and this warrants further investigation. Furthermore, it remains unknown if ICP during spaceflight needs to be pathologically elevated to cause the observed ocular changes, or whether the lack of diurnal variation in ICP typical of upright and supine posture on Earth is sufficient to alter CSF production rates.

## 9. *Choroidal Folds*

If the retrobulbar pressure becomes elevated beyond physiologic levels, the pressure may compress the posterior globe causing posterior sclera flattening thereby moving the macula anteriorly. Hence, posterior globe compression or sclera flattening may be a secondary mechanism contributing to the hyperopic shift. Scleral flattening may also contribute to choroidal fold development by decreasing the surface area that supports the choroidal vasculature. As a consequence, the choroidal vessels become compressed, precipitating folding.

Although not typically associated with the development of optic disc edema, choroidal folds have been reported in 11 of 47 (23.4%) crewmembers as demonstrated by either fundoscopy or OCT imaging. The anatomical location and presentation of these folds varies between individuals, with some folds appearing in a circular pattern around the optic disc and others appearing as horizontal folds between the disc and macula. Currently, choroidal folds visualized on fundoscopy or OCT are evaluated and graded on the following scale: clear (0), trace (1), mild (2), moderate (3), or severe (4). The pathophysiology surrounding this finding remains unknown at this time.

Choroidal folds usually involve Bruch's membrane and the adjacent RPE, but they may also be associated with retinal folding (Mader et al. 2017). The absence of vision changes with the occurrence of choroidal and retinal folding suggests that these folds have not been of sufficient magnitude, so far, to cause vision distortions. Any factor causing globe flattening or congestion within the choriocapillaris may lead to folding.

## 10. *Summary*

The constellation of ocular signs and symptoms reported during and after long-duration spaceflight, including optic disc edema, globe flattening, choroidal folds, enlargement of the subarachnoid space detected from ONSD distension, and a hyperopic shift are similar to those described in idiopathic intracranial hypertension. This led to the initial primary hypothesis that SANS resulted from elevated ICP. In contrast, more recent case reports suggest an alternative hypothesis that does not rely on pathologically elevated intracranial pressure for the development of SANS. This alternative hypothesis proposes that a localized rise in optic nerve sheath pressure within the orbit could occur even without a rise in ICP. Furthermore, invasive measurement of ICP during brief periods of weightlessness in parabolic flight (see below) support the notion that the acute headward fluid shift does not result in pathologically elevated ICP. Although the etiology remains unknown, it is proposed that SANS findings may represent manifestations of a pathologic process related to, but not limited to, the eye and the optic nerve, the brain, and the vascular system including venous congestion experienced during prolonged weightlessness.

### B. Analog Evidence

*1. Parabolic Flight, Effects on ICP and IOP*

No invasive direct measurements of ICP have been conducted during spaceflight, but many of the risks and considerations that would require resolution before attempting an ICP measurement during weightlessness have been reviewed (Barr 2014). Recent work by Lawley *et al.* (Lawley et al. 2017) utilized patients that had implanted Ommaya reservoirs for central nervous system chemotherapy administration, but were asymptomatic for at least 1 year, to directly measure ICP during ~20-second periods of weightlessness achieved during parabolic flight and referenced to both seated and supine positions. A fluid-filled 25 gauge needle was inserted into the Ommaya reservoir and attached to a pressure transducer to continuously measure ICP during posture changes and weightlessness during parabolic flight. ICP was $4 \pm 1$ mmHg while seated and increased to $15 \pm 2$ mmHg after stabilization in the supine position. In a separate experiment, these same subjects were in the supine position throughout parabolic flight and ICP decreased by $3.8 \pm 2.9$ mmHg after transitioning from $1g$ to $0g$. This indicated that ICP during weightlessness falls to levels between seated and supine values on Earth. These data led the authors to conclude that removal of the gravitational vector does not raise ICP to pathologically elevated levels.

Some have hypothesized that resistance exercise conducted as a countermeasure to muscle and bone loss during long-duration spaceflight may lead to periodic spikes in ICP and thus contribute to SANS signs and symptoms. The same patients with Ommaya reservoirs performed leg-press exercises during head down tilt (n=4) and during the weightlessness phase of parabolic flight (n=8) while conducting Valsalva and Mueller maneuvers (Lawley et al. 2017). Because of the slight increase in ambient $CO_2$ on the ISS these subjects were also exposed to 0.7% $CO_2$ during exercise and throughout 24 hours of 6° head-down tilt. Leg press exercise performed during weightlessness in parabolic flight with uncontrolled Valsalva significantly lowered ICP by a few mmHg compared to the ICP pressures in supine position in $1g$. In the supine and 6-degree head down tilt posture (after 5 min and 25 hr) central venous pressure and ICP increased during Valsalva with leg press contraction. During the Muller maneuver, the reduced intrathoracic pressure and central venous pressure during leg extension attenuated the magnitude of change of ICP.

Two groups of investigators have reported IOP increases during parabolic flight. Draeger and colleagues documented a mean 5 mm increase in IOP during the free-fall phase of parabolic flight using a hand-held applanation tonometer, which has been superseded by more accurate instruments (Draeger and Hanke 1986). Mader *et al.* (Mader et al. 1993) also measured IOP during parabolic flight using a TonoPen. They found that IOP increased 7 mmHg on average, from a mean baseline value of 12 mmHg to an in-flight mean of 19 mmHg (n = 11).

Recently IOP values obtained during parabolic flight were compared to IOP values during posture changes in a $1g$ environment (Anderson et al. 2016). Not only does IOP increase when moving from seated to supine, but a further increase occurs when subjects are positioned face down in the prone posture; during brief periods of weightlessness experienced in parabolic flight, IOP falls between the supine and prone values.

During weightlessness the loss in the gravitational vector that drains blood flow through the internal jugular vein may contribute to venous congestion and impair cerebral venous and lymphatic drainage from the skull. Noninvasive estimates of internal jugular venous pressure (IJVP) recently conducted during periods of weightlessness in parabolic flight using compression sonography in 11 healthy subjects (8 female) in a seated position indicate that IJVP during weightlessness ($23.9 \pm 5.6$ mmHg) is greater than IJVP during seated posture at $1g$ ($9.9 \pm 5.1$ mmHg) (Martin et al. 2016). Furthermore, when intrathoracic pressure is increased to 10 and 20 mmHg at $0g$ by having subjects perform a Valsalva maneuver, IJVP increases 10 and 20 mmHg, respectively.

In some cases of idiopathic intracranial hypertension (IIH), choroidal folds have been found to precede the development of optic disc edema. In others, choroidal folds have been the only presenting sign of raised ICP from any source (that is, pseudotumor cerebri, venous sinus thrombosis, or intracranial mass). This suggests that either elevated intrasheath pressure and indentation of the globe, or elevated venous pressures transmitted to the choroid may cause choroidal folds before the onset of optic disc edema. It may be possible that variation of elastic properties of the sclera in different individuals could have some influence on how readily globe flattening occurs. If ICP is raised, but doesn't reach a critical level to cause axoplasmic stasis for that individual, it may cause retrolaminar ONS enlargement and posterior globe flattening without causing obvious ONH swelling.

The inter-individual variability of the elastic properties of the ONS has been demonstrated by Hansen *et al.* (Hansen et al. 2011), while Lavinsky *et al.* (Lavinsky et al. 2007) showed variability among subjects in scleral rigidity as a determinant of the visible effects of the transmission of an increased ICP to the globe. In their study, they described the most frequent sonographic findings in IIH cases: flattening of the posterior ocular wall, thickening of the retinochoroid layer, and distension of the ONS. It is likely that in some individuals, retrobulbar pressure becomes great enough to cause some globe flattening, but not so high as to cause axoplasmic stasis. Even if the choroid is engorged due to ICP elevation, the sheath and lamina are likely flexible enough to minimize axonal compression, maintain axoplasmic flow, and help prevent swelling and disc edema.

## 2. *Head-down Tilt, Effects on ICP and IOP*

Direct invasive assessment of ICP in healthy subjects has not been performed during prolonged bed rest, but multiple studies have investigated the magnitude of change in ICP during various tilting postures. Table 1 presents a list of studies in which ICP was invasively measured in "healthy" control subjects via lumbar puncture, Ommaya reservoir, or a tip-transducer catheter passed into the brain parenchyma or the frontal horn of the right lateral ventricle (Edsbagge et al. 2004; Qvarlander et al. 2013; Petersen et al. 2016; Eklund et al. 2016; Lawley et al. 2017). We applied a random-effects meta-analysis to the data reported in these studies (number of subjects, mean, and standard deviation) and estimated an overall mean of 16.0 cm $H_2O$ and a 95% confidence interval of 14.9 to 17.2 cm $H_2O$ for healthy subjects in the supine position. However, the range for the mean ICP across these studies is 12.8 to 20.4 cm $H_2O$. In a subset of these studies, subjects were positioned at 6, 9, 10, or 20-degrees head-down tilt to measure the effect of a headward fluid shift on ICP. Using the same Ommaya reservoir patients that underwent

parabolic flight experiments, Lawley *et al.* (Lawley et al. 2017) measured ICP throughout 24 hours of 6° head-down tilt and found it was the same as ICP measured while supine before tilting (Lawley et al. 2017). Eklund *et al.* tilted subjects at a 9-degrees head-down tilt and ICP increased from 14.3 to 21.5 cm $H_2O$ while the subjects were supine (Eklund et al. 2016). Petersen *et al.* who reported the lowest supine ICP of 12.8 cm $H_2O$ tilted subjects to 10- and 20-degrees head-down tilt, which resulted in ICP increasing to 14.3 and 19 cm $H_2O$, respectively (Petersen et al. 2016).

**Table 1** Publications reporting invasive measurements of ICP in healthy subjects. n = number of subjects. AJPR, American Journal of Physiology, Regulatory, Integrative and Comparative Physiology; IOVS, Investigative Ophthalmology & Visual Science; JAP, Journal of Applied Physiology; NTG, normal tension glaucoma; OHT, ocular hypertension; POAG, primary open angle glaucoma. Note: Eklund *et al.* (2016) used 2 controls groups for appropriate matching to 2 disease populations.

| Publication | Position | n | Mean (SD), mmHg | Mean (SD), cm $H_2O$ | Subject Population |
|---|---|---|---|---|---|
| Eklund, Ann Neurol, (2016) 80:269-276 | Supine | 11 | 10.5 (1.5) | 14.3 (2.0) | Healthy adults |
| | Supine | 11 | 11.5 (0.8) | 15.6 (1.1) | Healthy adults |
| Berdahl, IOVS, (2008) 49:5412-18 | Supine | 68 | 12.7 (3.9) | 17.3 (5.3) | Age-matched control subjects for POAG and NTG (> 55 yrs) |
| | Supine | 39 | 11.5 (3.3) | 15.6 (4.5) | Age-matched control subjects for OHT (30-70 yrs) |
| Berdahl, Ophthalmology, (2008) 115:763-68 | Supine | 49 | 13.0 (4.2) | 17.7 (5.7) | Non-POAG |
| Ren, Ophthalmology, (2010) 117:259-66 | Supine | 71 | 12.9 (1.9) | 17.5 (2.6) | Non-Glaucoma |
| Petersen, AJPR, (2016) 310:R100-4 | Supine | 9 | 9.4 (3.8) | 12.8 (5.2) | Patients: non-surgical candidates, 18-70 yrs |
| Qvarlander, JAP, (2013) 115:1474-80 | Supine | 27 | 11 (2.1) | 15.0 (2.9) | Patients: investigation for suspected normal pressure hydrocephalus |
| Edsbagge, AJPR, (2004) 287:R1450-5 | Supine | 34 | 10 (2.3) | 13.6 (3.1) | Healthy medical or dental students. ICP Range: 9.2-19.1 cm H20 |
| Lawley, J Physiol, (2017) 595:2115-2127 | Supine | 8 | 15 (2) | 20.4 (2.7) | Former cancer patient free of disease for > 1yr |

While it remains unknown whether ICP would increase during more prolonged periods of head-down tilt, the lack of gross ocular changes after up to 70-days of head-down tilt bed rest suggests that bed rest does not increase ICP, or some other factor may occur that leads to a different response during prolonged bed rest than occurs during prolonged spaceflight. Lawley *et al.* suggested that the pillow that is placed under all bed rest subjects' heads may provide enough of a gravitational vector for blood and CSF to drain from the head and prevent an elevated ICP. In fact, ICP in supine subjects was reduced by an average of 4 mmHg when the head was lifted onto a pillow (14 ± 2 mmHg [without pillow] and 10 ± 2 mmHg [with pillow]). However, subtle increases in peripapillary retinal thickness (+4.67 µm ≤ mean delta +12.17 µm) in the inner sectors of the Early Treatment Diabetic Retinopathy Study (ETDRS) grid did develop after 70 days of head-down tilt bed rest (Taibbi et al. 2017). This thickening decreased with increasing distance from the optic disc such that average retinal nerve fiber layer thickness increased by just

+1.33 μm after bed rest and there were no differences between the control and exercise groups in any ocular measures.

Similar to the effects of posture change on ICP, IOP is also influenced by changes in body posture (Weinreb et al. 1984; Friberg and Weinreb 1985; Draeger and Hanke 1986; Mader et al. 1990; Liu et al. 1998, 2002, 2003a; Chiquet et al. 2003; Xu et al. 2010), the most common of which is the transition from the upright position to the supine posture. Using a noncontact tonometer, Chiquet *et al.* (Chiquet et al. 2003) measured IOP in 25 healthy female subjects who were seated as well as 1, 3, and 10 minutes after laying flat. After 1 minute in the supine position, their IOP had increased by 2 mmHg relative to sitting and then remained stable throughout the 10 minutes of monitoring. This observation of an elevation in IOP while supine is consistent with results from other studies (Wilson et al. 1993; Liu et al. 1998, 2002).

The first known study to examine the effects of prolonged simulated microgravity on ocular structure and function was reported in 1970 by Drozdova and Nesterenko (Drozdova and Nesterenko 1970). Sixteen healthy subjects were studied before, during, and after 70 days of bed rest. The specific conditions studied, which the authors refer to as "hypodynamia", were not clearly delineated in this report, but after 45 days of hypodynamia, visual acuity had decreased by 21%, the visual field decreased by 11 degrees, and the near point of clear vision had been extended by 3.5 cm. Interestingly, the authors reported that IOP decreased by 3 mmHg from a prestudy level of 20 mmHg. The authors reported that visual function had decreased further after 67 days of hypodynamia; the visual field decreasing by 15 degrees and the near point of clear vision had been extended by 12.5 cm relative to the prestudy measurement. The authors failed to indicate the timing of their ophthalmic examinations relative to the study timeline, but they reported that changes in visual function appeared to be coupled with structural changes within the eye. The optic disc appeared to have faded and the temporal borders were indistinct. Additionally, both the veins and the arteries of the eye appeared to be enlarged. In particular, the authors noted that the veins were distended and exhibited a deeper coloration. Encouragingly, the changes in the visual function and structure after 70 days of hypodynamia in the study by Drozdova and Nesterenko recovered somewhat when subjects resumed their normal activities (Drozdova and Nesterenko 1970). Twenty days after the end of the hypodynamia condition, ophthalmic examination revealed that the arteries of the eye had returned to their normal size, the veins were less distended, and the optic disk was pink with sharp boundaries. Concomitantly, visual acuity and the size of the visual field had recovered to some extent after 20 days but these were not at the prestudy baseline. Unfortunately, it appears that no follow-up examinations were completed beyond the 20 days post hypodynamia; therefore, this study does not provide any clues to whether these observed changes in vision and ocular structure were long lasting or permanent. While it is difficult to correlate these changes with spaceflight-induced alterations in vision with any certainty, it is relevant to note that vision changes in astronauts do not consistently resolve after long-duration spaceflight either (Mader et al. 2011).

In a study of 4 male subjects exposed to 120 days of horizontal bed rest, Kuzmin (Kuz'min 1973) found that IOP increased to 28 to 30 mmHg. In 2 of the subjects, the increase in IOP was accompanied by visual disorders in the form of clouding of vision and a decrease in visual acuity. Kuzmin proposed that impaired regulation of IOP was occurring under prolonged bed rest, and that subjects over 45 years of age and those with autonomic dysfunction could be at

increased risk of increased IOP. Similar changes in IOP were noted by Kuzmin *et al.* in a 62-day horizontal bed rest study (Kuz'min 1973).

The cephalad fluid shift during the transition from an upright to a head-down posture would be expected to result in even greater elevations in IOP compared to the transition to supine posture because the hydrostatic gradients are reversed compared to gradients when standing or sitting. In an extreme illustration, Draeger *et al*. (Draeger and Hanke 1986) observed that IOP, measured with the same hand-held applanation tonometer as the one used during spaceflight studies, almost tripled in 20 healthy volunteers when they moved from the +90° head-up position (~12 mmHg) to the -90° head-down position (~34 mmHg) in increments of 45°. Similar increases were observed by other investigators (Weinreb et al. 1984; Friberg and Weinreb 1985). As had been observed, IOP increases when subjects move from the head-up to supine posture, but the elevation in IOP was more dramatic once subjects progressed beyond the supine posture to head-down positions. The influence of the respective height of the hydrostatic column relative to the gravity vector is clear when measuring local pressure changes during posture transitions; changes in leg arterial pressures appear to be concurrent and inversely related to the alterations in IOP (Draeger and Hanke 1986). It must be noted, however, that acute radical tilts do not reflect a spaceflight analog condition and these results should be taken for their own relevance.

Therefore, because spaceflight conditions are not simulated by such extreme postures as inversion, it seems more reasonable to explore IOP effects during a more moderate head-down position. Draeger *et al*. (Draeger and Hanke 1986) examined 10 men during 90 minutes of 10-degree head down tilt (HDT). There was an immediate elevation of IOP with HDT that reached a maximum (~24 mmHg) after 15 minutes. IOP decreased somewhat by 45 minutes of HDT and was stable through the end of the tilt, although still higher than the level observed during the seated posture. Draeger *et al.* also observed that IOP decreased during lower body negative pressure used to reverse the cephalad fluid shift, and the pressure was restored when the decompression of the lower body was released. The effects of HDT on IOP were also present, although attenuated, when subjects were dehydrated by a sauna exposure that reduced their body weight by 2% before tilt. In this spaceflight model of induced plasma volume loss, the initial elevation of IOP was less severe and the peak pressure was acquired and resolved in a shorter time when subjects were dehydrated, but the pattern of intraocular responses to tilt remained. Also, using the 10-degree HDT model, Shinojima *et al.* measured subfoveal choroidal thickness and foveal retinal thickness. They hypothesized that elevated ophthalmic vein pressure during simulated microgravity increases subfoveal choroidal thickness via enlargement of the choroidal vasculature and greater choroidal blood volume. Subfoveal choroidal thickness and IOP were increased by HDT during simulated microgravity, although no change in foveal retinal thickness was observed (Shinojima et al. 2012).

Xu *et al.* (Xu et al. 2010) evaluated IOP in 65 males, with a mean age of 22.5 years, during 21 minutes of 15-degree HDT to assess whether myopic individuals were more sensitive to cephalad fluid shifts than emmetropes and low myopic subjects. Baseline mean values of IOP in the low myopic eyes and emmetropic eyes were similar (15.09 ± 3.20 mmHg and 14.71 ± 3.07 mmHg, respectively) while those in the moderate myopic eyes appeared slightly higher (16.59 ± 3.50 mmHg). During the 15-degree HDT, the mean value of IOP was increased in all subjects at every test point when compared to their respective baseline values. The IOP in the moderate

myopic group was higher than the IOP in the emmetropic and low myopic groups at 1, 6, and 11 minutes after the initiation of the 15-degree HDT test (*P*, 0.05), and reached a peak of 21 mmHg at 6 minutes. The results suggested that IOP in the moderate myopia group was more sensitive to postural change.

Mader *et al.* (Mader et al. 1990) examined IOP and visual acuity in 9 men aged 19 to 29 years during 48 hours of 10-degree HDT. The subjects showed a diurnal variation in IOP, with values lowest early in the morning and highest at noon. Baseline IOP was 11.2 mmHg while seated, and rose to 17.9 mmHg within seconds of subjects assuming the head-down position. When they sat up 48 hours later, IOP had decreased 6.7 mmHg on average. Because these two IOPs were significantly different, the authors concluded that a greater volume of blood was displaced at the end of the 48 hours than at time zero. In a companion study of the same subjects during this 10-degree HDT period, Frey *et al.* (Frey et al. 1993) reported a 4% increase in the size of the optic disc. Retinal artery and vein diameters were greater and IOPs were lower during the seated rest period before the subjects assumed the HDT posture, but no change occurred during bed rest. Additionally, as bed rest progressed, thoracic fluid volume decreased in these subjects along with a tendency for middle cerebral artery velocity to decrease. The decrease in middle cerebral artery velocities was inversely correlated with the change in retinal vasculature caliber. This observation agrees with reports from Friberg and Weinreb (Friberg and Weinreb 1985) of subjects during total body inversion (hanging upside-down). Chiquet et al. (Chiquet et al. 2003) measured IOP and corneal thickness in 8 women during and after 7 days of 6-degree HDT bed rest. In these subjects, IOP measured in the HDT position progressively decreased through the course of bed rest, becoming significantly lower than pre-bed rest values after 5 days of bed rest. IOP recovered to pre-bed rest levels after 2 days of normal activity.

Mader *et al.* (Mader et al. 2011) noted that an increase in episcleral venous pressure would elevate IOP due to backflow resistance. However, because aqueous flow is less than or equal to 3 µL/min (Goel et al. 2010), such a large increase in IOP would take several minutes to occur if it was purely a result of impaired aqueous humor outflow and would not lead to the observed rapid spike in IOP. This could, however, be explained by an engorgement of intraocular uveal tissue, principally the choroid, secondary to cephalad fluid shift. Normally, blood in the choroid is drained through the vortex veins. When the head remains in the recumbent position, venous blood may pool in the choroid owing to the effects of gravity. As the choroidal blood flow lacks autoregulation, there is little resistance to fluid accumulation aside from the tamponade effect of rising IOP. Total body inversion causes a sudden rise in choroidal blood volume of only 20 µL, which may result in an immediate rise in IOP of more than 20 mmHg (Smith and Lewis 1985). While the choroidal circulation is not autoregulated, the retinal circulation is believed to be autoregulated and is mainly influenced by local factors (Delaey and Van De Voorde 2000). Therefore, small fluctuations in choroidal blood volume during positional changes may cause sudden and significant increases in IOP.

Recent work investigating 3.5 hours exposure to tilt angles of 6°, 12°, and 18° HDT found that relative to the supine position, IOP increased 2.2 mmHg and 3.4 mmHg during 12° HDT and 18° HDT, respectively. Furthermore, application of 40 mmHg lower body negative pressure returned IOP to baseline values after each of these tilt angles (Marshall-Goebel et al. 2017a).

Although the cephalad fluid shift during transient changes in posture and the resulting influence on IOP is not unexpected, chronic head-down bed rest as a ground-based analog of weightlessness may be more relevant for determining effects in astronauts onboard ISS. The well-recognized diuresis secondary to HDT might modify or attenuate IOP during the course of bed rest, although the continued hydrostatic gradient may cause the choroidal vessels to fill and increase episcleral pressures (Draeger and Hanke 1986). The 6-degree head-down tilt bed rest model has been used as a ground-based analog for weightlessness, replicating many of the cardiovascular, muscle, and bone changes seen during spaceflight. After the seminal report of ocular structural and functional changes in astronauts, NASA implemented similar ocular assessments in subjects participating in prolonged bed rest studies. A case study of a 24 year old Caucasian male who spent 30 days in head-down tilt bed rest demonstrated a 28% decrease in intraocular pressure and a 17.4 and 21.4 micron increase in peripapillary retinal thickness in the right and left eye, respectively, compared to pre-bed rest values (Taibbi et al. 2013). Imaging taken 6 months after bed rest showed that thickness returned to pre-bed rest levels. IOP monitoring of bed rest subjects in 6-degree HDT for 14 days revealed that IOP increased from baseline by an average of 2.17 mmHg (right eye) and 2.06 mmHg (left eye) after 3 days of bed rest, and by 2.13 mmHg (right eye) and 1.74 mmHg (left eye) after 10 days of bed rest. After 2 days of bed rest, IOP was not different from pre-bed rest values (Taibbi et al. 2014). When IOP data were evaluated after 14-day (+1.4 mmHg) and 70-day (+1.8 mmHg) bed rest studies (Taibbi et al. 2016) the change appeared physiologically insignificant and called into question the effects of bed rest on IOP. This study also found a significantly greater increase in peripapillary retinal thickness following 70-days compared to 14-days of bed rest in the superior (+11.50 μm vs +4.69 μm), nasal (11.46 μm vs 4. 63 μm), and inferior (10.08 μm vs 4.34 μm) quadrants. Optic disc edema, choroidal folds, cotton wool spots, globe flattening, and changes in refractive error did not develop during these bed rest studies.

Taibbi *et al.* (Taibbi et al. 2014) evaluated best-corrected visual acuity (BCVA), spherical equivalent, IOP, spectral-domain OCT, retinal nerve fiber layer thickness (RNFLT), optic disc and macular parameters in 16 subjects (12 men and 4 women) before, during, and after 14 days of HDT bed rest. Equivalency tests revealed that nearly all post-bed rest changes were within predefined clinically relevant thresholds, suggesting that the experimental conditions did not significantly affect participants' visual function. However, there were small changes in the following parameters: BCVA (pre/post-BR mean difference: -0.06 logMAR), spherical equivalent (-0.30 D), IOP (+3.03 mmHg) and OCT (+1.14 μm), temporal inferior (+1.58 μm) and nasal-inferior RNFLT (+3.48 μm). In general, HDT bed rest resulted in a small non-progressive IOP elevation, which returned to baseline levels post-bed rest.

A short report by Mekjavic *et al.* (Mekjavic et al. 2002) examined the effects of longer bed rest on IOP and vision and reported no changes in visual function in any of the 10 subjects who participated in 35 days of horizontal bed rest. Unfortunately, the authors did not report whether IOP changed during this protocol, although they stated it was measured. However, interpretation of these results relative to other studies is hampered by two important factors. First, the measurements were not made until the second or third day after bed rest, during which time some recovery from bed rest may have occurred. Second, this was a horizontal bed rest, which acute studies have suggested does not have as dramatic an effect on IOP.

In conclusion, it is apparent that IOP is transiently elevated above the seated and supine pressures upon the assumption of the head-down posture; this change in posture models conditions of initial insertion into weightless in space. The rapid increase in IOP, concomitant with a cephalad fluid shift, has also been observed during the brief periods of weightlessness that are experienced in parabolic flight (Mader et al. 1993). However, available bed rest data suggest that elevated IOP resolves over time.

### 3. Modeling

Strain, stress, and stiffness of ocular tissues may play a role in the biomechanics of the optic nerve head. Ocular geometry and tissue material properties contribute to strain and stress of posterior ocular structures, for example at the ONH and the lamina cribrosa (LC). Both IOP and ICP can contribute to these tissue strains and stresses (Feola et al. 2016). Some factors that contribute to the ONH biomechanics are size and shape of the scleral canal, scleral thickness, regional laminar density, and collagen beam orientation. Therefore, eyes with identical IOPs may exhibit different strain fields because of differences in their structural stiffness (Bellezza et al. 2000). Recent work characterized the mechanical behavior of porcine optic nerve sheaths through inflation and axial loading that allowed for unconfined lengthening, twisting, and circumferential distension (Raykin et al. 2017). They reported a "cross-over point" in the pressure-diameter curves under varying axial loads and suggested this represented a protective behavior to prevent optic nerve compression.

Three primary tissue types are found in the ONH: load-bearing connective tissues of the peripapillary structures (sclera, scleral canal wall, and LC), axonal tissues (retinal ganglion cell axons), and cellular elements (astrocytes, glial cells, endothelial cells, and pericytes along with their basement membranes) (Bellezza et al. 2000).

Finite element modeling suggests that structural deformations at the vitreoretinal interface may not correspond with those at the anterior surface of the LC. In addition, scleral and laminar compliance may contribute more to average strains within the LC than compliance of neural and pia matter tissues (Sigal et al. 2004). Finite element modeling demonstrates that sclera stiffness has a large influence on ONH biomechanics (Sigal et al. 2005). The sclera is the primary load-bearing tissue of the eye, and less compliant than other ONH tissues. Alterations in scleral tissue properties can modify how the sclera responds to IOP or other pressures at the posterior of the eye, and therefore the less compliant structures at the ONH can be modified as well. High or heterogenous scleral strains may translate and impact tissues at the ONH, for example causing alterations in LC structure, compression of axons, and/or reduction in ONH microvascular blood and interstitial fluid flow (Downs et al. 2003). Indeed, modeling work suggests CSF pressure impacts the strain distribution within the LC and the retrolaminar neural tissue (Feola et al. 2017). Understanding how these models translate over longer periods of time will be necessary since certain ocular parameters appear to respond to changes in the gravitational vector over the course of 60 min (Anderson et al. 2017).

## C. Consequences

### 1. *During Spaceflight*

Although 24 individual crewmembers have demonstrated one or more structural or functional change consistent with SANS, none of these changes have been severe enough to endanger mission success. Many crewmembers alter the prescription of reading glasses during spaceflight, but additional 'consequences' of SANS remain absent.

### 2. *Following Spaceflight*

Prolonged optic disc edema may lead to long-term deleterious consequences for the optic nerve as has been seen in IIH patients. For example, evidence from IIH patients presenting with symptoms varying in duration from 1-30 months and a median CSF pressure of 34 cm $H_2O$ (range 10.9-61.2) suggests that those who regained normal disc appearance (50% of patients) following Diamox (acetazolamide) administration had a shorter duration of disease (median=4 months) and had better visual outcomes compared with those whose symptoms persisted longer (median=12 months). When followed for a median of 49 months, patients with chronic disc changes and higher grades of disc edema had an enlarged blind spot that was nearly 2 times larger than the area of the blind spot of patients who had lower grades of disc edema and who regained normal disc appearance over the follow-up period (Figure 20) (Sørensen et al. 1988).
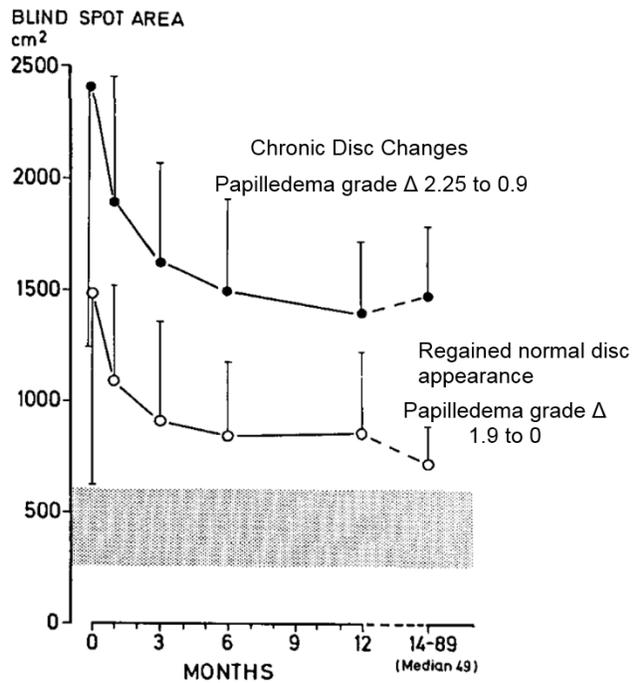


**Figure 20** *Blindspot enlargement in IIH patients with optic disc edema treated with acetazolamide.*

Additionally, in a study of 22 IIH patients with mild papilledema, a mean Frisen grade of 2 (range 1-3), a mean CSF pressure of 35 cm $H_2O$ (range 25.5-45), and a mean age of 40 years (Rebolleda and Muñoz-Negrete 2009), visual field (VF) perimetry testing at 1-year follow-up revealed that 66% had normal VF, 18% had an enlarged blind spot, and 16% had an irreversible

VF loss. On OCT, 10 subjects had an RNFL that was thinner than normal (3 of those had VF constriction, 3 had inferonasal defects, 1 had a scotoma).

VF assessment conducted within the first 3 days after astronauts return from space can identify whether optic disc edema contributes to an enlarged blind spot. Follow-up testing of OCT RNFL thickness should be conducted to identify whether the chronic optic disc edema during spaceflight leads to RNFL thinning during the years following spaceflight. VF testing should be done in conjunction with OCT imaging to identify whether functional deficits develop along with any structural changes.

## VI.    HYPOTHESIZED CONTRIBUTING FACTORS

The original leading hypothesis for the ocular changes documented in the astronauts affected by SANS was that the cephalad fluid shift caused by spaceflight exposure results in a prolonged increase in ICP. The symptoms (choroidal folds, globe flattening, cotton wool spot, hyperopic shift, and optic disc edema) seen in affected astronauts after long-duration spaceflight are similar to those seen in the terrestrial idiopathic intracranial hypertension (IIH) condition (Friedman 2007), yet the astronauts do not display all of the classic IIH symptoms such as chronic headaches, diplopia, transient visual obscurations, or pulse-synchronous tinnitus. Various hypotheses for the etiology of SANS signs and symptoms are discussed below.

### A.  Intracranial Pressure

The pressure-volume relationship between ICP, volume of CSF, blood, and brain tissue, is known as the Monro-Kellie doctrine (Mokri 2001). The cranium's constituents (blood, CSF, and brain tissue) maintain a homeostasis, such that any increase in volume of one of the cranial constituents must be compensated by a decrease in volume of another. However, a small buffering capacity exists for increases in intracranial volume primarily by the volume of CSF and to a lesser extent, the volume of venous blood. These buffers respond to increases in volume of the remaining intracranial constituents. For example, in a head trauma patient with an expanding epidural hematoma the increased mass will be compensated by the displacement of CSF and venous blood out of the cranium (Mokri 2001).

Intracranial pressure can be measured with direct insertion of a pressure transducer into the lateral ventricle of the brain, but it is often assessed via lumbar puncture while patients are positioned horizontally on their side. Because of the invasiveness required to access and measure ICP, few reports have provided measures in truly healthy populations, however, a pressure of 10-20 cm $H_2O$ is considered normal (Johanson et al. 2008) which agrees with the studies highlighted in Table 1.

### 1.  Similarities to IIH

Idiopathic intracranial hypertension (IIH), also known as pseudotumor cerebri, is a condition characterized by increased ICP without clinical, laboratory, or radiologic evidence of an intracranial space-occupying lesion, meningeal inflammation, or venous outflow obstruction. This increased ICP can lead to optic disc swelling (papilledema) caused by high CSF pressure in the distal optic nerve sheath, elevation of the pressure in the central retinal vein, and impaired perfusion of the neurons as their axons traverse the lamina cribrosa (LC) (Brazis and Lee 1998).

That astronauts have demonstrated globe flattening, ONSD distension, and optic disc edema highlights similarities with IIH patients. However, the fact that astronauts have not manifested other findings typically associated with IIH, including headaches, symmetric presentation of ocular findings, diplopia, and transient visual obscuration, supports the possibility of an alternative etiology.

## 2. *Hydrostatic Fluid Redistribution*

In a 1*g* environment, acceleration due to gravity creates a downward force that acts on the body's fluids. As a consequence, a hydrostatic pressure gradient exists across the body's axis, resulting in a higher pressure in the most dependent regions and lower pressure at the head. This is most evident in the standing position. The arterial pressure in a standing male of average height has been estimated to be 200 mmHg at the foot, and only 70 mmHg at the head (Hargens and Richardson 2009) (Figure 21). The venous blood is also subject to the hydrostatic gradient, and gravity assists cerebral venous drainage from the head, preventing cerebral venous congestion and elevations in ICP. Upon exposure to weightlessness and loss of the hydrostatic gradient, there is a cephalad fluid shift of 1-2 liters from the lower body. Consequently, arterial pressure across the body's axis equalizes so that pressure at the foot and the head is ~100 mmHg. Interestingly, Rowell reported that arterial pressure was approximately 98 mmHg at the foot and 99 mmHg at the head when supine (Rowell and Blackmon 1988). Thus, vascular, interstitial, and cerebral spinal fluids moves from the dependent regions to the abdomen, thorax, and head on a daily basis on Earth when a person assumes a supine position during sleep. Importantly, but often ignored, the CSF also shifts
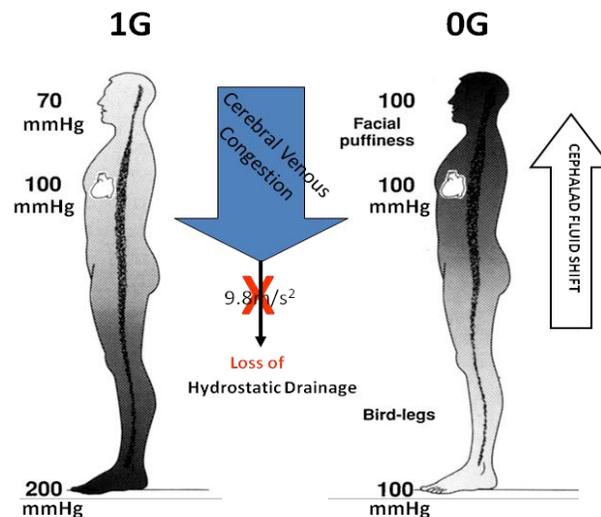


**Figure 21** Loss of hydrostatic pressure gradient drainage and cerebral venous congestion. Adapted from Hargens AR, et al. 2009, with permission of Elsevier BV, obtained via Copyright Clearance Center, Inc.

An indication of the changes in central and cerebral hemodynamics that occur as a result of fluid shifts during spaceflight may be illustrated by the terrestrial work of Chapman *et al.* (Chapman et al. 1990) and Hirvonen *et al.* (Hirvonen et al. 1995). Chapman (Chapman et al. 1990) inserted intraventricular catheters in a group of normal subjects and measured ICP while

tilting subjects at multiple angles. Similarly, Hirvonen and Kauko (Hirvonen et al. 1995) measured central venous pressure (CVP) in normal subjects at similar tilt angles. In the upright position (0 degree), ICP in a representative subject was found to be -2.3 mmHg (-3.1 cm $H_2O$), while Hirvonen and Kauko found the CVP to be 0 mmHg. In the supine position (90 degrees), ICP increased by 11.5 mmHg (15.6 cm $H_2O$) from -2.3 mmHg (-3.1 cm $H_2O$) to 9.2 mmHg (12.5 cm $H_2O$), and correspondingly, CVP in the same position increased from 0 to 5 mmHg. When subjects were placed in HDT (-30 degrees) ICP increased an additional 14.8 mmHg (20.1 cm $H_2O$) from the supine position to 24.0 mmHg (32.6 cm $H_2O$), while CVP in a similarly tilted subject increased to 9 mmHg. These invasive experiments document how cephalad fluid shifts affect CVP and ICP. In the case of ICP, the acute effect of cerebral venous engorgement is an increase in blood volume within the cranium. As the cranium is rigid and not expandable, pressure increases modestly, and within the normal limits of ICP (10 to 15 mmHg or 13 to 20 cm $H_2O$). However, in these experiments, subjects were tilted for brief periods lasting no longer than 5 to 15 minutes. In the case of the ISS astronauts, the fluid shift exposure is constant for approximately 5 to 6 months.

Upon entry into microgravity, the loss of the hydrostatic gradient results in a redistribution of fluid pressures across the body's axis causing an increase in venous pressures above the right atrium relative to standing in 1*g*. As described earlier, Hirvonen and Kauko (Hirvonen et al. 1995) showed an increase in CVP with fluid shift from standing to supine in terrestrial subjects, and Gisolf *et al.* (Gisolf et al. 2004) reported an increase in venous pressures from standing to supine of approximately 40 mmHg from -20 mmHg standing to 15 to 20 mmHg supine. The shift in venous volume to the cranium is at least partially responsible for the acute change in ICP, as demonstrated by Chapman (Chapman et al. 1990) and is illustrated by the equation for ICP:

$$ICP = CSF_{out\ flow\ resistance} \times CSF_{formation} + Superior\ Sagittal\ Sinus\ Pressure$$

Although increases in CSF outflow resistance will increase ICP, the most immediate increase will be venous volume shift into the dural venous sinuses. Underappreciated, however, is the shift of CSF from the spinal compartment into the cranium that likely occurs when the head to foot gravitational vector is removed during spaceflight. Evidence from MRI suggests cerebral ventricular volume increases from before to after spaceflight (Roberts et al. 2017). Whether this outcome is in response to the headward shift of CSF during spaceflight is unknown.

*3. Changes in CSF Regulation*

It has been proposed that alterations in the regulation of CSF contribute to changes in ICP during spaceflight, yet limited data exist in astronauts, all of which come from the postflight period when measurements may reflect processes responding to the re-adaptation to a 1*g* environment. Rats exposed to weightlessness during short-duration spaceflight provide some evidence of alterations in CSF production during weightlessness, but there is no evidence from long-duration spaceflight. While a complete review of CSF regulation is beyond the scope of this report, a recent review of CSF dynamics may be of help to the reader (Lawley et al. 2016).

The total volume of CSF in humans is estimated to be 150 to 270 mL, but because it is produced at a high rate of 0.3 to 0.6 mL/min, 500 to 600 mL of CSF is produced daily and is sufficient to completely replace the entire volume 3 to 4 times per day (Redzic and Segal 2004).

The pulsatile flow of CSF exits into the spinal and subarachnoid spaces through the fourth ventricle before passing into the cervical lymphatic system and draining into the venous blood. Normal CSF pressure in humans is approximately 10 to 20 cm $H_2O$, which is greater than the venous pressure in the dural sinuses (Johanson et al. 2008), and drives the flow of CSF out of the brain and into the systemic vasculature. For example, in the supine position, CSF pressure may be 10 to 12 mmHg (13.6 to 16.3 cm $H_2O$), whereas superior sagittal sinus pressure (SSP) may be 5 to 7 mmHg yielding a driving pressure of 3 to 5 mmHg for CSF reabsorption. Thus, an increase in the venous pressure of just a few mmHg could alter the diffusion gradient and inhibit CSF reabsorption. As a result of venous congestion and the associated increase in venous pressure, CSF reabsorption could be decreased causing an accumulation of intracranial CSF. However, the arachnoid granulations are now thought to have a role in regulating CSF drainage in times of increased pressure (Eklund et al. 2007; Johanson et al. 2008; Andersson et al. 2008).

The choroid plexus, located in the lateral, third and fourth ventricles, comprises cells that are specialized in the secretion of CSF and are regulated by multiple mechanisms, including protein expression and regulatory hormones. The apical membrane of choroidal epithelial cells contains aquaporin proteins and $Na^+/K^+$ ATPase pumps, which facilitate fluid transport in the choroid plexus and support CSF production, as well as receptors for atrial natriuretic protein (ANP) and arginine vasopressin (AVP), which regulate volume.

Short-duration spaceflight and analog models have been used to study the effects of weightlessness on choroid plexus, aquaporin-1 (AQP1) channels, and hormonal regulation of CSF production (Gabrion et al. 1995, 1996; Mani-Ponset et al. 1997; Davet et al. 1998; Carcenac et al. 1999). During the Space Life Sciences-2 experiments aboard the STS-58 mission, rats sacrificed on flight day 13 of a 14-day mission demonstrated a modified structure of apical microvilli of the choroid plexus (Gabrion et al. 1996), indicating structural changes to cells important in regulating CSF production. Additionally, the ratio of AQP1 concentration to the total choroidal surface area (AQP1/ChT) was decreased in rats dissected 6 to 8 hours after return to Earth ($9.2 \pm 0.9$) compared to ground control animals ($25.5 \pm 1.7$), suggesting a likely decrease in CSF production (Masseguin et al. 2000). Hormonal regulation of CSF also appears to be altered by spaceflight. ANP receptors at the choroid plexus of the lateral and third ventricles increased after rats returned from short-duration spaceflight (Herbuté et al. 1994), and pituitary concentrations of AVP decreased after return from spaceflights of 7 to 14 days, relative to values in vivarium control rats ($6.3 \pm 0.3$ vs. $8.3 \pm 0.5$ µg/mg tissue (Wade and Keil 1998). Because ANP blunts water permeability of AQP1 (Patil et al. 1997) and AVP stimulates AQP1-dependent water transport and increases choroidal CSF secretion (Patil et al. 1997), these data support the hypothesis that CSF production is down-regulated during short-duration spaceflight. Additionally, immunodetection of carbonic anhydrase II in the cytoplasm of choroidal cells was reduced in the flight animals, which would result in a down-regulation of CSF formation.

Interestingly, animals dissected 48 hours after return to Earth demonstrated a 48.4% overshoot of AQP1 expression, ($37.8 \pm 4.5$ AQP1/ChT, p<0.04) when compared to values in

control animals (AQP1/ChT = 25.5 ± 1.7) (Masseguin et al. 2000) and recovery of microvilli structural changes at the apical surface of choroidal cell membranes (Davet et al. 1998). These data indicate that the rebound and overshoot of factors regulating CSF production occur during the first few days upon return to a 1$g$ environment and may play a role in the elevated lumbar puncture opening pressures observed in a number of U.S astronauts > 2 days after returning from a long-duration spaceflight.

To date, 10 U.S. astronauts have developed disc edema during flight. Five of these astronauts had mildly elevated postflight CSF lumbar puncture opening pressures despite removal from the precipitating environment. We hypothesize that the flight animals and astronauts develop an elevated ICP setpoint secondary to prolonged weightlessness exposure. Upon return to the 1$g$ environment and re-exposure to a hydrostatic gradient, sagittal sinus pressure (SSP) is suddenly reduced and ICP falls, thus causing an upregulation of CSF formation. This is supported by the histological and biochemical changes in the flight animals that cause an overshoot of CSF production in comparison to baseline and could explain the mildly elevated CSF pressure detected in 5 US astronauts during their re-adaptation to a 1$g$ environment. Therefore, astronauts may be at risk for persistently elevated ICP in the postflight period.

## 4. *Venous Congestion*

The superior ophthalmic vein and the much smaller inferior ophthalmic vein merge to drain into the cavernous sinus and drain fluid from the eye. Because the venous system from the eye has no valves, impaired venous outflow or even retrograde flow may occur in the face of elevated pressures transmitted from the cavernous sinus. Elevated ICP and venous pressures can be transmitted to the eye via the ophthalmic vein along 3 pathways. The most significant is via the choroidal veins that drain blood from the choroid, a rich vascular network that lies between the outer sclera of the eye and the inner retina. The choroidal veins drain into the vortex veins that subsequently drain into the superior and inferior ophthalmic veins. Almost the entire blood supply of the eye comes from the choroidal vessels. Thus, relatively large shifts in volume can occur and thereby alter IOP. According to Smith and Lewis (Smith and Lewis 1985), 20 μL of additional blood volume in the choroid can increase IOP up to 20 mmHg.

The second pathway is via the episcleral veins that lie within the sclera and drain the percolated aqueous humor from the anterior chamber after it passes through the trabecular meshwork. The episcleral veins drain both indirectly into the vortex veins via the anterior ciliary veins, and directly into the vortex veins, which drain into the superior and inferior ophthalmic veins. It is well known from the study of glaucoma that elevations in episcleral venous pressure cause a direct rise in IOP due to the decreased facility (outflow) of aqueous humor via the trabecular meshwork, thereby increasing the pressure within the anterior chamber of the eye (Craven 2008). As noted previously, this is a slow process that can take 20 minutes or more to occur. In contrast, choroidal engorgement may cause a spike in IOP within seconds. In summary, episcleral venous pressure is influenced by venous drainage pressure in the superior/inferior ophthalmic veins, cavernous sinus, and even internal and external jugular veins, a contributing mechanism for rising IOP in the supine position (Liu et al. 1998). Thus, any abnormality leading to increased venous pressure in the venous drainage system downstream from the eye can lead to elevated IOP if the episcleral venous pressure is increased as occurs in

jugular vein obstruction, superior vena cava obstruction and cavernous sinus thrombosis (Craven 2008).

The third and most minimal route of transmission of elevated venous pressure and ICP is via the central retinal vein (CRV). The effect of CRV engorgement on IOP is likely minimal; however, rising retinal vein pressures can cause retinal hemorrhages. The CRV drains venous blood from the retina. The CRV exits the eye alongside the retinal artery through the optic nerve before exiting the subarachnoid space and the optic nerve sheath. Beyond that point, it has several anatomical variations and may join the superior or sometimes the inferior ophthalmic vein, or less often the cavernous sinus directly (Hayreh 2006). The CRV is also directly influenced by ICP during its course through the subarachnoid space within the optic nerve sheath.

To identify how elevated superior vena cava pressure may affect ICP and ONSD, Nusbaum *et al.* developed a juvenile piglet model of elevated superior vena cava pressure (SVCP) by increasing SVCP to 20 and 40 mmHg for 1 hour each by inflating a balloon catheter placed within the super vena cava (Nusbaum et al. 2013). Serial measurements of ICP (interventricular drain catheter placed 4mm later and rostral to the bregma through a craniotomy), internal and external jugular pressure (IJP, EJP, respectively; venous catheter) were made hourly for 3 h, and ONSD of the right eye was measured hourly by ultrasound (US). Naive piglets were maintained at baseline pressure levels for 3 h and measurements of dynamic ICP were made continuously for the entire period in a similar fashion to the SVCP occlusion group. In the naive piglets, ONSD did not change significantly over time. Interestingly, there was a significant linear correlation between IJP and ICP (slope: $0.9614 \pm 0.0038$, r =0.9683). Moreover, with increasing SVCP, resulting ONSD was also correlated with ICP (slope: $0.0958 \pm 0.0061$, r $= 0.7841$), suggesting that for every 1 mmHg increase in ICP there was a 0.1 mm increase in ONSD. Sensitivity and specificity for ONSD in diagnosing elevated ICP were 92% and 91%, respectively, for a cutoff of 5.45 mm. However, external validation of these findings in humans is required to understand the physiological significance of these relationships across the range of ICP values that likely occur during weightlessness.

## 5. *Cerebral Edema*

The Starling-Landis equation describes the net balance of hydrostatic and oncotic pressures within the intravascular and extravascular fluid at the level of the capillaries, which are known as Starling forces (Hargens and Richardson 2009). An increase in venous pressure due to venous congestion will alter this balance of pressures by increasing transcapillary pressure and result in net filtration of fluid to the brain parenchyma. If this occurs, brain parenchyma swells and in turn increases sinus venous pressure. This phenomenon underlies the development of high altitude cerebral edema (Wilson et al. 2009). In addition to potential changes in Starling forces during exposure to weightlessness, changes in the integrity of the blood-brain barrier, based on the tightness of the endothelial cell-cell tight junctions in the walls of the intracranial capillary vessels, could also contribute to cerebral edema. While there is no direct evidence of alterations in tight junctions in astronauts, rats subjected to hindlimb suspension for 30 and 180 minutes demonstrated no change in tight junctions found between choroid plexus epithelial cells and that tight junction structure and protein composition were unaltered, as confirmed by freeze-fracture and conventional electron microscopy, and immunohistochemistry for typical tight junction

proteins, respectively (Masseguin et al. 2001). Further assessment of tight junction permeability was confirmed by showing that cytochrome C injected into the blood circulation did not cross the blood-CSF barrier at the level of the choroid plexus. Whether the hindlimb-unloading model in rats for up to 3 hr can be extrapolated to human exposure to the weightlessness environment of spaceflight for up to 6 months is unknown. In-flight investigations of fluid distribution and postflight MRI targeting extravascular fluid are needed to definitively determine if fluid accumulates during long-duration spaceflight. While gravitational unloading of body tissues and fluids, one of the most pervasive changes caused by weightlessness during spaceflight, may have an ability to alter the integrity of the blood-brain barrier, exposure to higher levels of radiation in space may also affect the biology of endothelial cells in a way that will reduce the integrity of the tight junctions. The effect of radiation exposure similar to that on the ISS on blood-brain barrier function remains poorly studied.

*6.  Optic Disc Edema*

Optic disc edema is often associated with an increase in ICP (in which case it is referred to as papilledema), and is characterized by deformation of the ONH and swelling of the optic disc, which often protrudes into the eye globe. Optic disc edema has been observed in 10 American and US-partnered astronauts manifesting visual alterations after return from long-duration missions.

If the ICP rises because of an increase of cerebrospinal fluid volume, the pressure gradient will point unidirectionally from the chiasmal cistern to the subarachnoid space of the optic nerve in the manner of a hydraulic pump, building up pressure in the small compartment that ends blindly behind the globe. Intracranial CSF reaches the orbital subarachnoid space (SAS) in a "cul-de-sac" anatomy at the optic nerve head (Figure 22). The SAS contains a complex system of arachnoid trabeculae and septa that divide the SAS into different segments and thus the hydrodynamics of the CSF within the SAS may not simply reflect a continuum of pressure along a tube (Killer et al. 2003). Structurally, the immediate retrobulbar space is more distensible due to the absence of pillars and septae found in the less distensible intraorbital and canalicular portions of the optic nerve sheath. These features are believed to be important for pressure homeostasis. This arrangement facilitates the flow of CSF within the optic nerve SAS allowing a buildup of physiologic pressure within the retrobulbar space and thereby facilitating periodic reverse flow and thus circulation of CSF.
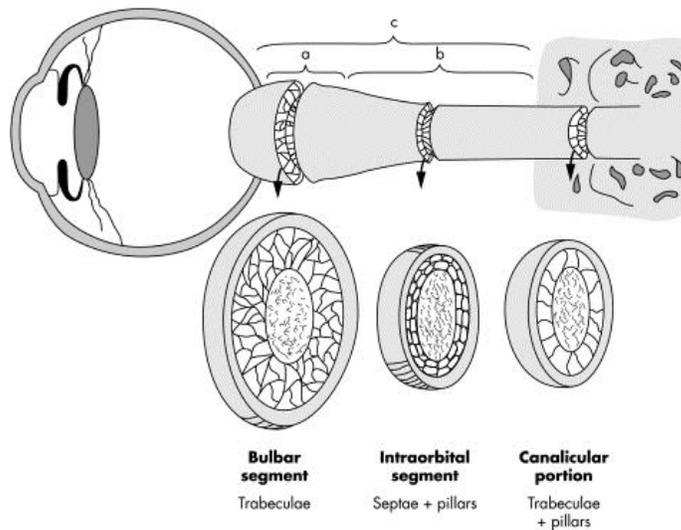
**Figure 22** *Schematic drawing of the optic nerve demonstrating the microanatomy of the ONS complex. Reproduced from Killer HE, et al. Ophthalmol, 2003 with permission from BMJ Publishing Group Ltd.*

Measurements of decreasing pressure along the optic nerve SAS in a proximal to distal direction (Liu and Kahn 1993), suggest that the subarachnoid space may not have a pressure equivalent to that of the ventricles, the cisterns, and the cranial subarachnoid spaces. Thus, while, correlations between ICP in IIH patients and ONSD provide evidence that elevated pressure is transmitted to the SAS, this relationship and exact influence in the development of optic disc edema remains incompletely understood. Furthermore, it is unknown if increases in ICP are transmitted to the ONH during weightlessness to the same degree as occurs in a 1$g$ environment. Yet, measures of ONSD from MRI provide the opportunity to assess the effects of HDT on this ocular parameter and possible countermeasures. After 4.5 hours of 12° HDT ONSD increased significantly compared to the supine position, but lower body negative pressure of 20 mmHg during HDT prevented this increase (Marshall-Goebel et al. 2017c). Data collected from this same study (Marshall-Goebel et al. 2017b) suggested that DTI-derived diffusivity parameters and fractional anisotropy were enhanced during various degrees of HDT compared to the supine position, suggesting alterations in CSF hydrodynamics and increased CSF volume within the optic nerve sheath (Gerlach et al. 2017).

ICP can affect the ONH in diseases such as pseudotumor cerebri, a condition in which the ICP is greater than IOP, resulting in swelling of the ONH. In addition to this protrusion, local edema within the optic papilla may develop due to tissue ischemia, an increased pressure gradient between the SAS and the vitreous of the globe with resultant transarachnoid transudation of fluid, and/or the extravasation of fluid secondary to this pressure gradient (Jinkins 1987). A significant factor in the proximate cause of early edema is stagnant axonal transport (stasis) with added vascular congestion, leakage, and ischemia leading to disc swelling (Tso and Hayreh 1977). When severe swelling or edema occurs within the SAS occurs, neural and vascular structures become compressed and distorted to varying degrees, and venous drainage is believed to be compromised, thus leading to stasis. Several investigators report that the demonstrated axonal swelling is a response to the increased pressure gradient and axoplasmic stasis (Jinkins 1987; Berdahl and Allingham 2010). Preliminary data analyzed from eyes

obtained from female 10 to 12 week-old BALB/Cj mice following short-duration spaceflight suggest upregulation of genes associated with oxidative stress in the retina and optic nerve (Zanello et al. 2013). Swelling of the ONH can also occur in ocular hypotony, which occurs due to a low IOP rather than elevated ICP. In both conditions ONH changes are caused by an increase in translaminar pressure. Investigating optic nerve biomechanics to understand the stress (force/cross-sectional area) and strain (local deformation) on the ONH (Burgoyne et al. 2005; Sigal et al. 2005) may yield clues as to the determinants of axonal, glial, and vascular dysfunction in the pathogenesis and progression of glaucoma and optic disc edema.

An important question is the relationship between the increase in ICP and the degree of distention of the ONS. Hansen and Helmke performed a study in twelve patients undergoing neurological testing that involved CSF absorption (Hansen and Helmke 1997). The ONSD was evaluated by serial B-mode ultrasound scans of the anterior optic nerve near its entry into the globe. The linear relationship between ONSD and ICP was only present within a certain CSF pressure interval. This interval differed between patients. ONSD dilation commenced at pressure thresholds between 15 mmHg (20.4 cm $H_2O$) and 30 mmHg (40.8 cm $H_2O$) and, in some patients, saturation of the response (constant ONS diameter) occurred between 30 mmHg (40.8 cm $H_2O$) and 40 mmHg (54.4 cm $H_2O$). Because of the variable pressure-diameter relationship, at higher CSF pressure levels the ONS may lose its ability for further dilation. Trabecular fibers and sheath collagen structure may determine this aspect of the sheath response. In Hansen's study, this certain threshold CSF pressure was, on average, 22 mmHg (30 cm $H_2O$) in all patients. The largest diameters were observed in the subgroup with the highest ICP readings (6.5 mm ONS diameter equivalent to 30 to 55 mmHg ICP or 40.8 to 74.8 cm $H_2O$).

Thus, the clinical relevance of this study relies on the demonstration of pathologically enlarged sheaths or ongoing enlargement on serial ultrasonography studies. This study also points to a possible threshold ICP before which changes in ONSD may not occur, or may not reflect ICP. At higher pressure, ONS distension reaches a saturation level at which the other papilledema-like features begin to manifest. Whether ICP has reached this threshold or surpassed a saturation point in astronauts is not clear and makes it challenging to interpret ONSD measurements in a meaningful way.

In their more recent work, Hansen *et al.* (Hansen et al. 2011) showed that prolonged dysregulation of ICP led to persisting dilatation of the CSF compartment surrounding the optic nerve. As with any nonelastic behavior, ONSD returned to baseline only when SAS pressures did not exceed 35 mmHg (47.5 cm $H_2O$). When decompression occurred from higher pressure levels (45 mmHg or 61.2 cm $H_2O$ and above), a clear residual dilatation remained (above 0.34 mm). Thus, after exposure to pathologically elevated pressures within the SAS, there is a limited capability for retraction of the optic nerve sheath after pressure normalization. When deformation due to over-distension occurs, a pressure-dependent structural remodeling in the trabecular tissue and∕or the dural elements takes place, reducing the retraction of the ONS to baseline levels when pressures are elevated above a certain threshold value and length of time. According to this study, direct correlation between distension and pressure exists for pressure values between 5 and 45 mmHg (6.8 to 61.2 cm $H_2O$).

Jinkins (Jinkins 1987) examined 20 subjects with increased ICP and papilledema, and found bulging of the optic sheath in the SAS in 18 of them, regardless of the cause of ICP. It was determined that dilatation of the sheath surrounding the optic nerve resulted in a "ballooning" of the ONH, causing it to protrude into the globe. This resulted in an increased pressure gradient between the SAS and the vitreous with resultant transarachnoid transudation of fluid secondary to the pressure gradient, possibly into the optic disc and the vitreous of the globe. Thus, a significant factor in early disc swelling or papilledema is papillary protrusion. Of note, Jinkins reported that protrusion precedes any obvious arterial abnormality in the optic disc and that such changes in the pressure gradient manifest rapidly, appearing within the first 24 hours of increased ICP. Thus, data collection close to the 24-hour mark of entry into weightlessness may be an important benchmark. Conversely, 4 ISS astronauts have manifested a refractive change $\geq$0.75 D in at least one eye, yet had no evidence of optic disc edema.

## 7. *Globe Flattening*

Determination of globe flattening in astronauts is currently limited to subjective analysis of globe morphology during the clinical read of the ocular MRI. While this rudimentary approach has provided insight into globe flattening prevalence following long-duration spaceflight, quantitative assessment of globe flattening may provide greater sensitivity and reliability in determining the development and progression or regression of SANS signs.

Alperin *et al.* (Alperin et al. 2013) have developed a quantitative assessment of globe flattening, nerve protrusion, and maximal deformation by creating a 2-dimensional (2D) map of the distances from the globe center to the posterior wall. The proposed automated method transforms the 3D globe geometry into a 2D color-coded quantitative distance map of the sclera in the posterior globe. This provides a distinctive advantage over scrolling through individual magnetic resonance (MR) images along different planes to appreciate 3D globe deformation.

The automated method for quantifying the 3D geometry of the posterior sclera involved the following steps: 1) segmentation, 2) identification of a reference point (center of globe), and 3) generating a 2D map of the distances from the globe center to the posterior wall. The centers of mass of the globe and the lens are identified and are used to define an orthogonal coordinate system in which the x axis (optical axis) is the posterior-anterior orientation, and the y-axis is oriented laterally from left to right.

Each point on the globe posterior wall is identified by use of 3 parameters: *d*, the distance in millimeters from the globe center; $\theta$, the azimuth angle (in the xy plane); and $\phi$, the elevation angle (in the xz plane), where $\theta$ and $\phi$ range from -90° to +90°. Color mapping is used to indicate shorter distances from the center and longer distances at the periphery. A 2D map of a perfectly spherical hemisphere will have a uniform color with a distance equal to its radius.

Three measures of globe deformation are calculated by using the distance map: 1) nerve protrusion (NP), depicting the extent of the nerve head protrusion; 2) globe flatness (GF), depicting the degree of flattening of the posterior wall, and 3) maximal deformation (MD), depicting the combined deformation due to the flattening and the nerve protrusion. Each measure is defined as the ratio of the mean distances within a central and a peripheral region in the 2D distance map.

Seven IIH patients with a mean CSF opening pressure of $36.9 \pm 7.8$ cm $H_2O$ (range, 26–47 cm $H_2O$) and bilateral papilledema (mean grade of 2.0) and 6 age- and sex-matched control subjects were examined for MRI evidence of GF. Compared to control subjects, mean values of the 3 deformation measures were significantly poorer in the IIH group, with nerve protrusion demonstrating the strongest difference ($P = .0002$). Nerve protrusion was most strongly associated with papilledema grade ($P=.01$) and maximal deformation was negatively associated with CSF opening pressure ($R=0.86$, $P =.0001$). Although both the NP and the GF measures were significantly worse in the IIH cohort, the NP measure more strongly separated the patients with IIH from the healthy control subjects.

The NP measure was also the one that was significantly associated with the clinical papilledema grading. On the basis of these observations and results, optic nerve protrusion may be a more clinically relevant marker for the risk of papilledema in IIH (Alperin et al. 2013) and a potential objective measure of papilledema severity compared with the subjective Frisen scale.

Analysis of globe distance maps for a subgroup of IIH patients treated with acetazolamide demonstrated reversal of the eye globe deformation. After only 2 weeks of treatment, there was a significant improvement in NP from 0.91 to 0.94, p=0.036 (Alperin et al. 2013).

There was also a significant correlation between the deformation measures and the CSF opening pressure. This is expected because the primary cause for the globe deformation in this population was increased CSF pressure transmitted to the globe through the increased CSF volume within the subarachnoid space and optic nerve sheath. This is consistent with the fact that MD, the combined deformation caused by NP and GF, demonstrated the strongest negative correlation with the CSF opening pressure, with an $R$ value of 0.86.
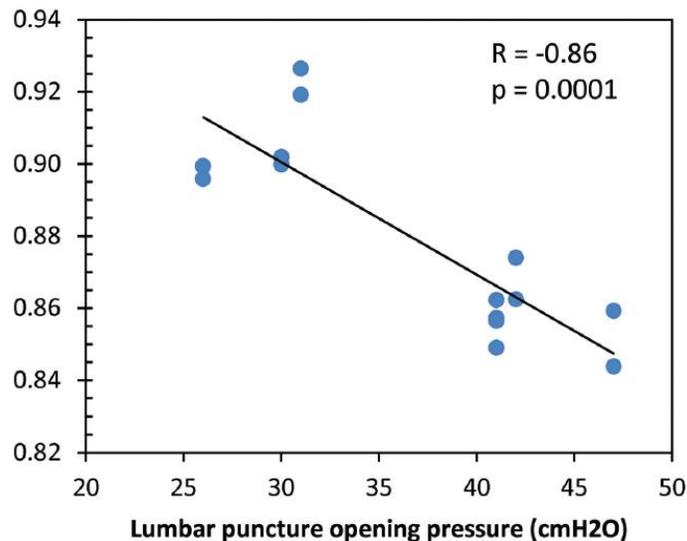


**Figure 23** *Scatterplot of the relationships between MD (y-axis) and CSF opening pressure (x-axis).*

The relationship demonstrated in Figure 23 represents an encouraging step towards quantification of globe deformation and the potential to improve the grading of SANS cases. Yet,

because no astronauts have had a lumbar puncture opening pressure greater than 29 cm $H_2O$, it is unclear whether this technique has the sensitivity to detect the degree of globe deformation present in astronauts, which may be less than that occurring in the IIH patients studied by Alperin.

*8.   Headache*

Since the Apollo Program missions, anecdotal reports of headaches due to cephalad fluid shifts have been documented. Indeed, a feeling of "fullness" of the head, or facial edema lasting for the duration of the flight were reported by all Apollo astronauts. Several crewmembers complained of symptoms such as headaches, congested sinuses, head pressure, pressure on the eyeballs, awareness of neck pulse, and distended veins in the forehead and neck (Hoffler and Johnson 1975). One Apollo astronaut described the fluid shifts as "the eye sockets themselves become a little puffy, the face a little rounder and a little redder, veins in the neck and forehead become distended and one's sinuses feel congested." The headaches were reported as frontal and occipital, and ranged in intensity from moderate, severe, to "one of the worst ever experienced." The headaches began as soon as crewmembers started moving about the cabin and ranged in duration from 3-4 days to mission duration. For instance, one crewmember reported that the "eyes gradually cleared but the congested sinuses, while not too bothersome, were always there." (Hoffler and Johnson 1975).

A more recent study found that headaches are still commonly reported among astronauts. Vein *et al.* (Vein et al. 2009) evaluated headache severity and incidence at 4 time points: (1) launch (period between the launch of space vehicle and docking to the space station), (2) stay at the space station, (3) activity outside the space station (extravehicular activity [EVA]) and (4) landing (between undocking from the space station and landing) in short duration (n=9; up to 2 weeks; mean 10.9 days; range 8–14 days) and long-duration (n=8; mean 201.7 days; range 150–366 days) astronauts. Vein *et al.* found that of the 16 male and one female astronauts who participated in the survey, 12 (71%) reported having experienced at least one headache episode while in space, whereas they had not suffered from headache when on Earth. There were in total 21 space headache episodes reported, of moderate to severe intensity in 71%. In 2 astronauts (12%) the headache and associated symptoms would match the ICHD-II criteria for migraine and in 3 astronauts (18%) for tension-type headache; in 12 astronauts (70%) the headache was non-specific. The vast majority of headache episodes (76%) were not associated with symptoms of space motion sickness (SMS). The 12 astronauts with headache reported a total of 21 headache episodes: 9 during launch, 9 during the stay at the space station, 1 during EVA and 2 during the landing. Headache severity ranged from mild to severe, with mild intensity in 29% and moderate to severe intensity in 71%, but was usually reported as moderate (65%). In 77% of the episodes, the headache was described as "exploding" and/or as "a heavy feeling" by 8 out of 9 astronauts during the launch, by 7 out of nine during the stay at the space station, by 1 astronaut during the EVA and by 2 out of 2 during the landing. When each independent headache episode was assessed, 16 (76%) demonstrated no association with the main symptoms of SMS, such as nausea, vomiting, or vertigo suggesting an etiology other than SMS.

Several non-pharmacological and pharmacological interventions have been used to mitigate headaches. For example, Apollo astronauts noted the effects of exercise, diet, and diurnal variation: "We always felt a lot better for about a half hour to 2 hours after we exercised

on the bicycle." The effectiveness of exercise in drawing blood away from the head was noted in Skylab missions, where a half inch increase in calf circumference was noted immediately following exercise (Johnston and Dietlein 1976). This strongly suggests the caudal movement of blood into the larger muscles of the lower limbs alleviating cerebral venous congestion. Additional reports indicated that symptoms of headache and head fullness were lessened following meals. Again, this suggests increased splanchnic blood flow alleviated venous congestion. The last effect is associated with the time of day. "As on Earth, if one is bothered by something, it typically feels worse toward the end of the day; the same was true up there with the sensation of head fullness" (Hoffler and Johnson 1975). In Apollo missions, several crewmen took Actifed to relieve nasal congestion at various times throughout the flight, whereas 64% of short- and long-duration astronauts reported taking analgesics for headaches (Hoffler and Johnson 1975).

## 9. Noninvasive Assessment of ICP

Owing to the hypothesis that elevated ICP may be a contributing factor for SANS, over the past few years a number of noninvasive devices have been investigated by NASA and others to estimate ICP in astronauts aboard the ISS, as well as during ground-based analogs such as head-down tilt.

The Cochlear and Cerebral Fluid Pressure (CCFP) Analyzer is currently onboard the ISS and is used to collect data as part of the Fluid Shifts experiment during weightlessness and during use of the Russian lower-body negative pressure device known as Chibis. Since the perilymphatic fluid of the inner ear communicates with the CSF of the brain, alterations in CSF pressure are transmitted to the perilymphatic fluid and affect tympanic membrane displacement in response to a loud tone. The CCFP device quantifies tympanic membrane displacement (Samuel et al. 1998a; b) to estimate changes in ICP, but does not provide an absolute pressure value. Before and after long-duration spaceflight, astronauts are studied in the seated, supine, and 15° HDT positions, while in-flight measures occur early and late in-flight, with and without application of lower-body negative pressure. The CCFP was recently used in a ground based study to demonstrate that 15° HDT posture induces a headward fluid shift and elevation of ICP which is reversed by 28% and 38% using 25 and 50 mmHg lower body negative pressure, respectively (Watkins et al. 2017).

The otoacoustic emission (OAE) technique is also based on the notion that the CSF communicates with the inner ear perilymphatic fluids. Alterations in CSF pressure alter oval window stiffness, which can be detected through alterations in acoustic signals emitted by oscillation of the inner ear auditory apparatus in response to different audible tones. Repeatable changes in distortion product OAE magnitudes, phase shifts, and power reflectance when subjects are tilted to 45° HDT, which presumably increases their ICP (Voss et al. 2010). Distortion product OAE was used to assess changes in ICP in patients undergoing diagnostic CSF infusion testing where ICP was increased in steps of 3 mmHg (Williams et al. 2016). Distortion product OAE detected significant changes in angle, and to a lesser degree magnitude, when ICP was ≥ 12 mmHg above baseline supine values.

The Vittamed two-depth transcranial Doppler device has shown promise in providing a noninvasive quantitative measure of ICP. The technology is based on simultaneously measuring

the blood flow velocity waveform in the intracranial and extracranial portions of the ophthalmic artery (OA) before, during, and after discrete increases in pressure applied to the closed eye. The pressure surrounding the intracranial portion of the OA is equal to ICP, whereas the extracranial portion of the OA lies outside of the cranial vault, in the orbit, and therefore is subjected to orbital tissue pressure. The device relies on the assumption that applied external pressure at which the waveforms of the internal and external OA match is equivalent to ICP (Ragauskas et al. 2005). Direct assessment of ICP in neurological patients undergoing lumbar puncture and simultaneous assessment with the Vittamed device resulted in 98% limits of agreement between the two methods spanning -4.0 to +4.0 mmHg when the mean opening pressure was 13.18 mmHg (± 2.99) with a range of 4.14 to 24.26 mmHg (Ragauskas et al. 2008). However, more recent work funded by the National Space Biomedical Research Institute in support of NASA produced much larger 95% limits of agreement between the two methods of -10.5 to +11.0 mmHg (Bershad et al. 2016). The mean LP opening pressure was 20.9 mmHg (9.8 to 28.6 mmHg) and some of the subjects were suspected of having IIH. The authors concluded that the wide limits of agreement indicated that the device should not serve as the only method of determining ICP in a given patient.

While not a direct measure of ICP, the sensitivity of optical coherence tomography has shown promise in detected changes in ICP. Patients undergoing lumbar puncture had a fall in ICP from $34.3 \pm 11.8$ cm $H_2O$ to $11.6 \pm 3.3$ cm $H_2O$ after removal of CSF. Concurrently, there was a decrease in the retinal pigment epithelium/Bruch's membrane angle in all subjects and a decrease in papillary height in 3 out of 5 subjects (Anand et al. 2016). Whether or not structural changes from OCT taken during spaceflight are sensitive enough to track smaller changes in ICP remains to be determined.

## B. Intraocular Pressure

Intraocular pressure is determined by the production, circulation and drainage of ocular aqueous humor and is described by the equation:

$$IOP = F/C + PV$$

where F=aqueous fluid formation rate, C = aqueous outflow rate, and PV = episcleral venous pressure.

In the general population, IOP ranges between 10 and 20 mmHg with an average of 15.5 mmHg (Liu et al. 1998). Diurnal variation for normal eyes is between 3 and 6 mmHg, with a nocturnal peak independent of body position change (Figure 24) (Liu et al. 1998, 2003a; Mosaed et al. 2005). Besides circadian variation, IOP has been shown to increase by 3 to 4 mmHg in both normal and glaucomatous patients lying supine, regardless of the time of the day (Liu et al. 2003b). Tilting to 15° head-down tilt also increases IOP, while application of lower body negative pressure significantly reduces it towards supine levels (Macias et al. 2015).
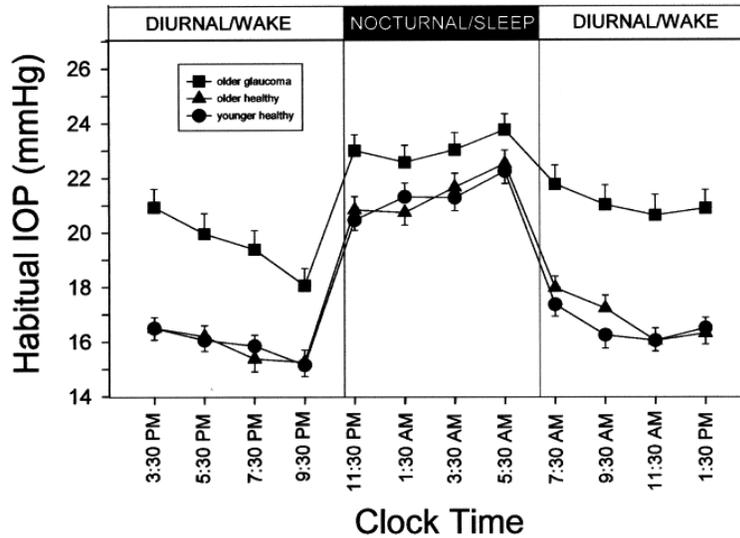


**Figure 24** *Correlation between office and peak nocturnal IOP in healthy subjects and glaucoma patients. Reproduced from Mosaed S, Liu JHK, Weinreb RN, with permission from Elsevier, obtained via Copyright Clearance Center, Inc.*

Twenty-four hour assessment in glaucoma and sleep studies (Mosaed et al. 2005) evidenced that IOP peaks roughly around 5:00 to 5:30 in the morning (during sleep period), and aging has a shifting effect delaying the peak post awakening (Mansouri et al. 2012). Aqueous humor flow also demonstrates a circadian rhythm, peaking in the morning at ~2.3 to 3.0 µl/min and dropping to 1.1 to 1.5 µl/min at night (Sit et al. 2008; Goel et al. 2010; Nau et al. 2013). There are two drainage routes for aqueous humor. The majority (up to 80%) is through the trabecular meshwork consisting of the uveal and corneoscleral meshwork, the endothelial lining of Schlemm's canal, and the collecting channels and aqueous veins. After having passed through the trabecular outflow pathways, aqueous humor drains into the episcleral venous system. The second drainage route is via the uveoscleral outflow pathway that is less defined and understood. Fluid in this pathway ultimately drains into the lymphatic system. Compared to 20-30 year old subjects, those older than 60 years have reduced aqueous humor production and uveoscleral outflow (Toris et al. 1999).

Episcleral venous pressure in healthy humans is in the range of 7 to 14 mmHg with values between 9 to 10 mmHg typically (Phelps and Armaly 1978). This is the only component of aqueous humor dynamics that is affected by body position. Episcleral venous pressure increases by 3.6 mmHg by changing body position from seated to supine. Any increase in episcleral venous pressure results in decreased trabecular meshwork aqueous outflow and a

corresponding increase in IOP. In fact, a change in episcleral venous pressure of 0.8 mmHg corresponds to a change in IOP of 1 mmHg. Moreover, trabecular and uveoscleral outflow is reduced in ocular hypertension.

Ocular hypertension, generally considered as an IOP greater than 21 mmHg, is the most important risk for glaucoma. The Ocular Hypertension Treatment Study showed that the incidence of glaucomatous damage in subjects with ocular hypertension was up to 3% for IOPs of 21 to 25 mmHg, up to 26% for IOPs of 26 to 30 mmHg, and approximately 42% for subjects with an IOP higher than 30 mmHg (Gordon et al. 2002). Age greater than 40 years is a risk factor for the development of both ocular hypertension and primary open-angle glaucoma. However, while in-flight monitoring of IOP using Tonopen had occurred as a part of routine medical monitoring on all astronauts, the relatively high variability in measurements and general lack of IOP values suggestive of ocular hypertension led to the cessation of acquiring this measurement. Currently, in-flight measurements of IOP occur as part of certain research experiments and as clinically indicated.

## 1. *Translaminar Pressure Difference*

In a 1-G environment under normal physiologic conditions, the difference between IOP and the retrolaminar CSF is the translaminar pressure difference (TLPD) that generates both a net posterior force on the surface of the lamina cribrosa (LC) and a hydrostatic pressure gradient within the neural and connective tissues of the prelaminar and laminar regions. The clinical importance of TLPD has gained in importance both in patients with elevated ICP and glaucoma patients with elevated IOP.

Jonas *et al.* (Jonas et al. 2004) suggested that the border between the high pressure intraocular space and lower pressure retrobulbar space produces a translaminar pressure gradient which can play a role in ocular disease if either pressure becomes abnormally high or abnormally low (Morgan et al. 1998, 2002). The TLPD depends on the difference in pressure and the thickness of the LC, thus Jonas *et al.* suggested one may infer that the reduced thickness of the LC in highly myopic eyes might be the histologic correlate of an increased susceptibility to glaucoma.

The TLPD is dynamic and not a static pressure difference, for example both IOP and ICP are altered during postural adjustments. In addition, both the IOP and ICP contain characteristic pulse pressure waveforms corresponding to the cardiac cycle. To accurately estimate the TLPD, both IOP and ICP should be measured with subjects in the same position, yet clinical assessments of ICP typically occur with patients in the supine or lateral side lying position, while IOP is typically measured in the seated upright position. Recent work by Eklund *et al.* in 11 healthy subjects demonstrated that both ICP and IOP change during posture changes, resulting in TLPD differences of 19.8 mmHg while seated, 12.3 mmHg while supine, and 6.6 mmHg while in the 9° head-down tilt position (Eklund et al. 2016). By assuming 16 hours of upright posture and 8 hours of supine posture per day, these authors estimated a 24 hr average TLPD of 17.3 mmHg. Conversely, estimates of TLPD during weightlessness when all hydrostatic pressures are removed suggest that during spaceflight TLPD is 6.7 mmHg, a decrease over a 24 hr period relative to pressures that occur on Earth.

Potentially, one could utilize the TLPD to guide treatment of optic disc edema by monitoring and modulating IOP and ICP. Pharmaceutical treatments aimed at ICP and IOP could rebalance the TLPD gradient thereby reversing axonal compression and edema formation. However, at present there is no validated method of noninvasively measuring ICP during spaceflight or providing such a countermeasure.

## 2. *Lamina Cribrosa*

Nerve fiber bundles from the optic nerve pass through the lamina cribrosa (LC) before entering the posterior pole of the eye. The LC is a porous, collagenous cylindrical structure at the bottom of the intrapapillary region (Figure 25 (Burgoyne et al. 2005)) and is composed of type-1, III, IV, V, and VI collagen, and elastin (Hernandez et al. 1987; Goldbaum et al. 1989). The human lamina cribrosa marks an important anatomical transition zone where axonal bundles anterior to the disc are not myelinated, but as they cross into the retrolaminar region become myelinated (Tso and Hayreh 1977; Hayreh 2016). This transition zone includes non-myelinated axons, therefore this tissue may be particularly susceptible to abnormal translaminar pressure differences and associated mechanical forces.

The LC shows regional variations. Pore size increases with increasing distance from the center of the LC (Figure 25); the largest pores are located close to the lamina margin, with the least amount of inner pore connective tissue in the inferior, superior, and temporal disc regions, and higher retinal nerve fiber count in the inferior and superior disc regions. In addition, the central portion of the lamina cribrosa tends to have a slight anterior elevation at the site were the central retinal vessel passes. There is evidence that high myopia is associated with a thinner and elongated LC (Jonas et al. 2004) and variations in the thickness of the LC and surrounding tissue has been hypothesized to increase stresses and strains from the higher translaminar pressure gradient (Sigal et al. 2004). During aging, weakening of the collagen within the LC alters its mechanical behavior, compromising the support of nerve axons that pass through it, and likely increasing the susceptibility of retinal ganglion cell axons to damage (Albon et al. 1995, 2000; Karwatowski et al. 1995). The change in mechanical compliance appears to be most marked after 40 to 50 years, the age at which the incidence of primary open angle glaucoma (POAG) is increased. This corresponds with the age range for astronauts affected with SANS.
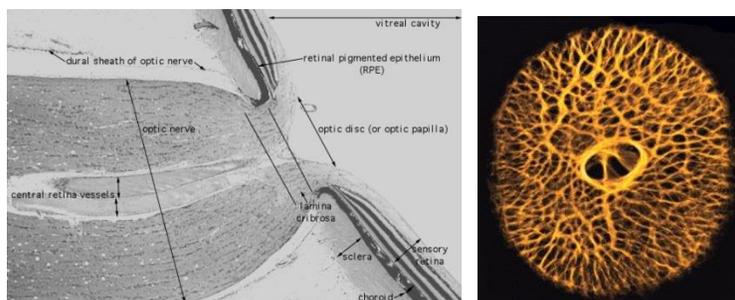


**Figure 25** *Left: Optic nerve and ONH X-Section. Reproduced with permission from Vaughan DW. Right: Anterior view LC. Reproduced from Burgoyne CF, et al., with permission of Pergamon, obtained via Copyright Clearance Center, Inc.*

Anatomical regional strain and stress distribution about the lamina cribrosa exist (Roberts et al. 2010) and alterations in these fields may be associated with quadrant based changes in

RNFL. While direct experimental measures of lamina cribrosa are limited, future advances in OCT imaging may provide future data to monitor lamina cribrosa structure. Because the stress on the ocular tissue of the globe, and thus at the LC, is related to the radius, larger eyes may have a greater cupping of the LC and thus greater stress on that tissue. As such, individuals with a large globe diameter may be at greater risk for damage to the LC and/or glaucomatous damage.

## C. Genetic

### 1. 1-Carbon Metabolism

Smith, Zwart, and others have put forward the theory that the incidence of ophthalmic issues is genetically predisposed (Zwart et al. 2017). This is based on initial findings related to differences in 1-carbon pathway biochemistry between crewmembers. In their initial paper, Zwart *et al.* (Zwart et al. 2012) identified differences in circulating concentrations of the folate and B12-dependent 1-carbon metabolic pathway between astronauts on ISS missions of 48–215 d with (n = 5) and without (n = 15) ophthalmic changes. They found that serum homocysteine (Hcy), cystathionine, 2-methylcitric acid (2MCA), and methylmalonic acid concentrations were 25-45% higher (P < 0.001) in astronauts with ophthalmic changes than in those without them, and that these differences were present before, during, and after flight. Moreover, preflight serum concentrations of Hcy and cystathionine, and mean in-flight serum folate, were correlated with change (postflight relative to preflight) in cycloplegic refraction (P < 0.05). Zwart and colleagues hypothesized that the higher Hcy may be caused by single-nucleotide polymorphisms of enzymes involved in folate- and vitamin B-12 dependent 1-carbon metabolism (Zwart et al. 2012). In a follow-on investigation, Zwart et al. (Zwart et al. 2016) examined whether genetic variations in 1-carbon metabolism genes (methionine synthase reductase (MTRR), methylenetetrahydrofolate reductase (MTHFR), serine hydroxymethyltransferase (SHMT), and cystathionine β-synthase (CBS)) contributed to susceptibility to ophthalmic changes in 49 astronauts (48 ± 4 yrs; 58-382 days in space). Results indicated that B-vitamin status and the number of risk alleles of the genes studied were significant predictors of many of the ophthalmic outcomes. Astronauts with the recessive G MTRR 66 allele had a higher risk of choroidal folds and cotton wool spots, and those with the SHMT 1420 C allele had a higher risk of optic disc edema after spaceflight. Additionally, preflight dehydroepiandrosterone was positively associated with cotton wool spots, and serum testosterone response during flight was associated with refractive change. Altered 1-carbon metabolism is likely one of many factors during spaceflight that contribute to endothelial dysfunction and vascular permeability that can increase an individual's susceptibility during flight. Mild hyperhomocysteinemia has been shown to increase arterial permeability and rigidity in animal models, and with a methylenetetrahydrofolate reductase (MTHFR) polymorphism, the blood concentration of folate is lower, promoting an increase in vascular permeability (Symons et al. 2006; Mullick et al. 2006), and ultimately potentially increasing ICP. Studies are currently underway to investigate a wider array of single nucleotide polymorphisms in the 1-carbon metabolic pathway. In addition, a terrestrial clinical population was identified as having similar characteristics to astronauts with ophthalmic issues, and a full characterization of that population is currently being conducted, with the hope that this may provide a terrestrial analog population in which to study astronaut ophthalmic issues. Whether these genotypes and resulting biochemical and physiological differences are associated with the mechanisms leading to astronaut ophthalmic issues or

whether they constitute genetic markers for other potential genetic associations is unknown and requires further investigation.

## 2. Biomarkers

There are several potential biomarkers in CSF and possibly in blood or other body fluids that may in the future be used for early detection of SANS or to identify astronauts with increased risk for developing the syndrome. The Panel members of the 2010 Visual Impairment Summit suggested several biomarkers as potential candidates including S-100, platelet count, albumin, CRP/inflammation markers, insulin-like growth factor, somatostatin, tet-transactivator (TTA), myelin basic protein, immunoglobin G index, oligo-clonal bands, atrial naturetic peptide, vasopressin, and aquaporin. In addition, gene expression profiling, epigenetic modifications of gene expression, proteomics, metabolomics, $CO_2$ retaining variants, single nucleotide polymorphisms, and copy number variants should be expanded to better characterize the individual susceptibility to develop SANS. As the etiology of the symptoms is more clearly defined the appropriate biomarkers will be evaluated.

## D. Spaceflight Exposures

### 1. Exercise

Exercise is an important countermeasure used to maintain muscle, bone, and cardiac health during spaceflight. Historically, Russian scientists have used a variety of exercise hardware and in-flight exercise protocols during long-duration spaceflight (up to and beyond 1 year) onboard the Mir space station. On the ISS, a combination of resistive and aerobic exercise is used. For missions to the moon, establishment of a lunar base, and interplanetary travel to Mars or to an asteroid, the functional requirements for physical human performance during each specific phase of these missions have not been sufficiently defined to determine whether currently developed exercise countermeasures are adequate. Long-duration missions and exploration missions with several transitions between gravitational environments present the greatest challenges to risk mitigation and to development of countermeasures of proven efficacy.

Despite its benefits on skeletal morphology and function, the effects of resistive exercise on the development of elevated ICP remain controversial. Recent work by Lawley, *et al.* demonstrated an acute increase in ICP during resistive exercise in weightlessness of parabolic flight (Lawley et al. 2017). When the subject simultaneously exercised and performed a Valsalva maneuver there was a concomitant increase in arterial blood pressure, central venous pressure, and ICP. Conversely, performance of a Mueller maneuver reduced central venous pressure and ICP to a similar magnitude during the resistive exercise task. Haykowsky *et al.* invasively examined ICP in fully cooperative, alert, and clinically stable patients who received a ventricular drain as part of their surgical procedure and postoperative care. They reported that resistive exercise without a Valsalva maneuver resulted in no change in peak systolic pressure or ICP (Haykowsky et al. 2003).

The effects of resistive exercise on IOP are less controversial. Resistive exercise training induces an increase in IOP (Lempert et al. 1967). A significant increase in IOP was also reported immediately after a static squat done until voluntary termination (Movaffaghy et al. 1998), and

during bench press (Vieira et al. 2006). A dramatic increase in IOP (115%) was observed in experienced strength trained subjects during a maximal static muscle contraction combined with Valsalva maneuver (Dickerman et al. 1999). However, IOP was decreased after static muscular actions, such as handgrip exercise in subjects with normal IOP values (Marcus et al. 1974). After exercising, IOP declined to 14% less than the pre-exercise values (Movaffaghy et al. 1998). The only study that incorporated dynamic muscular contractions reported that IOP was reduced 40% after a series of isokinetic muscular actions in subjects with normal IOP (Avunduk et al. 1999). More recently, Chromiak et al. demonstrated that IOP decreases after one or more sets of chest press and leg press performed at moderate intensity (Chromiak et al. 2003). Consequently, it appears as though resistance exercise performed without a Valsalva maneuver will not elevate ICP or IOP during exercise, and may even decrease ocular and cranial pressures post exercise.

In contrast to numerous investigations examining the effects of resistive exercise on cranial pressures, there is a dearth of information regarding the consequences of aerobic exercise on ICP. To our knowledge the only study to examine ICP during aerobic exercise invasively measured ICP in patients with normal and increased ICP (Brimioulle et al. 1997). The researchers found that exercise tended to decrease ICP both in patients with intracranial hypertension and in those with normal ICP. They suggested that because aerobic exercise is generally conducted without Valsalva maneuvers, it is unlikely that ICP will increase during such exercise. However, other studies have demonstrated that in both animals and humans global brain blood flow increases 20% to 30% during the transition from rest to moderate exercise (Kashimada et al. 1995; Delp et al. 2001). Interestingly, more recent work has shown that an increase in exercise intensity up to ~60% VO$_2$max results in an increase in CBF, after which CBF decreases toward baseline values (sometimes decreasing below baseline values) with increasing exercise intensity (Jørgensen et al. 1992b; a; Moraine et al. 1993; Hellström et al. 1996). These findings suggest that high intensity exercise may be a key countermeasure to decrease CBF and thus potentially ICP.

It is well established that IOP decreases transiently with aerobic exercise in proportion to intensity and duration (Figure 26) (Harris et al. 1994). For example, sedentary subjects' IOP reduced 28% immediately after cycling at a low intensity for 1 hour (Qureshi 1996), and individuals with elevated IOP (18 mmHg or greater) had a reduced IOP after a single bout of
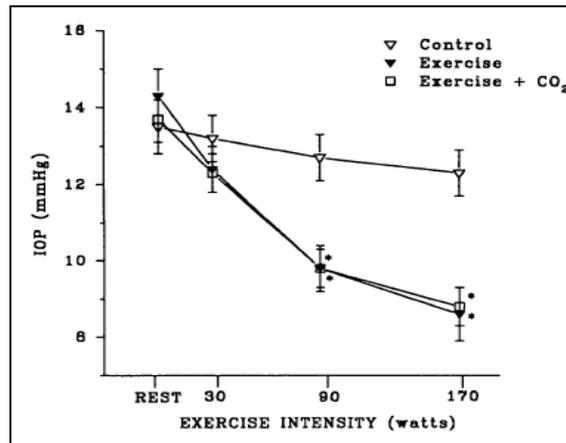


**Figure 26** *Impact of aerobic exercise on IOP. Reproduced from Harris A, and others, with permission of the Association for Research in Vision and Ophthalmology, obtained via Copyright Clearance Center, Inc.*

aerobic exercise (Qureshi 1996) and in individuals with elevated IOP (18 mmHg or greater) it was reduced after a single bout of aerobic exercise (Qureshi 1995). Another investigation demonstrated that IOP was decreased by 30% after an incremental cycle test to exhaustion in subjects with IOP values of 22 mmHg or greater (Passo et al. 1991). A ground-based study currently underway is assessing IOP during and immediately following high intensity resistive exercise and aerobic exercise during HDT.

## 2. Carbon Dioxide

### a) Elevated $CO_2$ on ISS

Carbon dioxide constitutes just 0.04% by volume of Earth's atmosphere, resulting in a partial pressure of $CO_2$ ($PCO_2$) of 0.3 mmHg at sea level. As a byproduct of metabolic respiration, humans expire $CO_2$ with each breath, which increases ambient $PCO_2$ in closed or poorly-ventilated environments if not adequately removed. As a result, indoor levels of $CO_2$ on Earth are typically elevated to ~1 mmHg. The Occupational Safety and Health Administration sets the maximum daily exposure limit for an 8-h work day to a time-weighted average of 0.5% (3.5 mmHg) (NIOSH 2007) despite the fact that the Environmental Protection Agency recognizes no acute effects for indefinite exposures of up to 1% $CO_2$ (7.5 mmHg) (Compressed Gas Association 1990). The Spaceflight Maximum Allowable Concentration (SMAC) for ambient $CO_2$ is set to 5 mmHg, although recent concerns related to reports of crewmember symptoms has led NASA to target levels equal to or below 4 mmHg (Law et al. 2014).

Elevated arterial $PCO_2$ leads to vasodilation of cerebral arteries to effectively "wash out" $CO_2$ from the brain, while augmented ventilation expels $CO_2$ from the body (Battisti-Charbonney et al. 2011). Despite these acute ventilatory and cardiovascular responses designed to rid the body of excess $CO_2$, it is unknown if chronic exposure to a mildly elevated $CO_2$ environment, combined with the headward fluid shift induced by weightlessness, contributes to the structural and functional changes characteristic of SANS. Ambient levels of $CO_2$ are elevated on ISS because of poor air convection, variability in $CO_2$ production from up to 6 crewmembers in an enclosed environment, and limitations with currently available $CO_2$ removal hardware. One hypothesis for the lack of SANS symptoms developing in ground analogs of spaceflight is that these models lack the elevated ambient $CO_2$ that is present on the ISS. Negative sequelae normally associated with high levels of $CO_2$ may result from the strong vasodilating effect of $CO_2$ include headaches, blurred vision, lethargy, irritability, and neurocognitive deficits. While these symptoms typically manifest in environments on Earth with high levels of $CO_2$ (typically greater than 5.0% inspired) (Henning et al. 1990; Law et al. 2014), it is unknown if the chronic exposure to mildly elevated $CO_2$ (currently ISS is <0.5% $CO_2$ inspired) experienced by crewmembers on ISS in combination with weightlessness or other spaceflight factors contributes to SANS or contributes to other negative impacts on crew performance, such as reductions in cognitive function (Manzey and Lorenz 1998a; b) or sleep (Barger et al. 2014).

### b) Localized Pockets

Because air convection is significantly reduced in microgravity, local pockets of $CO_2$ may develop around the nose and mouth. A computational fluid dynamics analysis revealed that without adequate ventilation, $PCO_2$ could rise above 9 mmHg within 10 minutes around a

sleeping astronaut's mouth and chin (Son et al. 2002). Fans built into the sleep quarters and directed at the astronaut's face are in place to prevent this buildup of $CO_2$.

Few investigations to date have measured true $CO_2$ exposures during spaceflight. The Major Constituent Analyzer (MCA) draws air from fixed locations that may not necessarily reflect local $CO_2$ levels around astronauts as they move throughout the ISS. Even the portable $CO_2$ monitors (CDMs) are generally placed on cabin walls and not directly next to the crew. In other words, CDM data may not be representative of what the crew truly experiences throughout their day. Portable wearable $CO_2$ monitors were recently launched to the ISS in 2016 and will hopefully provide more precise insight into the true $CO_2$ exposure of astronauts.

All in all, more data are needed to further the understanding of individual and environmental factors that contribute to $CO_2$-related symptoms in microgravity. It may be that certain individuals or one sex is more susceptible to $CO_2$ retention and increased ICP, but until true exposure data are available to correlate symptoms and $ppCO_2$, no conclusion can be drawn at this time about $CO_2$ susceptibility in spaceflight.

c)   *Acute $CO_2$ Exposure with Head-down Tilt*

Recent investigations into the combined effects of a headward fluid shift induced by HDT combined with elevated inspired $PCO_2$ provide evidence of acute exposures similar to what crewmembers may experience during prolonged spaceflight. Subjects who breathed 1% $CO_2$ for up to 60 min in the 6-degree HDT position had a small, but statistically significant increase in end-tidal $PCO_2$ as compared to values obtained when they breathed room air (42.1 mmHg vs. 40.4 mmHg, respectively). This increase was likely physiologically insignificant as there was no difference in mean blood flow velocity through the middle cerebral artery or noninvasively estimated ICP (Laurie et al. 2017). Similarly, using a double-blind cross-over design, blood flow through the internal carotid arteries measured using MRI was not different after 26.5 hours of 12-degree HDT breathing either room air or 0.5% $CO_2$ (Kramer et al. 2017), and noninvasive assessment of ICP using the Vittamed device revealed no difference in ICP in subjects exposed to 3.5 hours of 12-degree HDT breathing either room air or 1% $CO_2$ (Marshall-Goebel et al. 2017a) or during 24 hours exposure to 12-degree HDT breathing either room air or 0.5% $CO_2$ (Strangman et al. 2017).

d)   *Prolonged $CO_2$ Exposure*

No blood gas measurements of arterial $PCO_2$ have been measured in astronauts on ISS and only sparse measures of end-tidal $PCO_2$ ($P_{ET}CO_2$) have been reported as a surrogate. Prisk and colleagues reported $P_{ET}CO_2$ levels in crewmembers during long-duration spaceflight (Expeditions 3 to 6) were $39.0 \pm 3.9$ mm Hg, which was no different from supine levels measured before ($39.7 \pm 3.1$ mmHg) and after ($38.5 \pm 3.7$ mmHg) spaceflight (Prisk et al. 2006). Importantly, standing $P_{ET}CO_2$ levels were also measured before ($36.7 \pm 3.6$ mmHg) and after spaceflight ($35.5 \pm 4.3$ mmHg), highlighting the slight increase that occurs when transitioning from standing to supine due to the upward shift of the diaphragm and abdominal contents. A recent ISS experiment "BP Reg", showed that $P_{ET}CO_2$ was $42.1 \pm 3.7$ mmHg in 9 male subjects when ambient inspired $PCO_2$ averaged 3.8 mm Hg, which was significantly greater than the preflight seated value of $36.0 \pm 3.2$ mmHg (Hughson et al. 2016b). These data are combined in Figure 27.
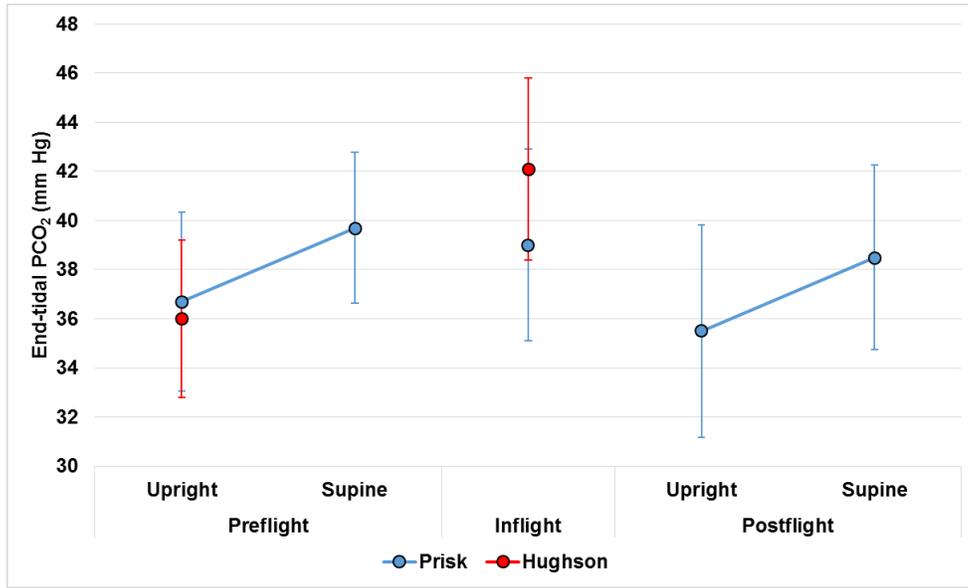
**Figure 27** *End-tidal $PCO_2$ measured pre-, in-, and postflight to the ISS. Data modified from Prisk et al. (2006) and Hughson et al. (2016). Values are means ± SD.*

Law and colleagues recently reviewed ISS $CO_2$ levels and de-identified astronaut private medical conference reports and reported an association between 7-day average $CO_2$ concentrations and headache incidence (Law et al. 2014). However, they found no association between $CO_2$ levels and vision changes. From Expedition 2 through 31 the average 24-h $CO_2$ concentration was 3.4 mmHg and the 7-day average $CO_2$ levels over a period from 2001 through 2012 was similar (Figure 28).

Prolonged exposure to a mild hypercapnic environment has been studied in a few subjects, although these subjects were lacking the headward fluid shift associated with spaceflight. Terrestrial exposure to 1.5% $CO_2$ for 42 days led to an elevation in alveolar $PCO_2$ of 2-3 mmHg in 21 subjects and increased minute ventilation ($V_E$) during the first few days of hypercapnia. With chronic $CO_2$ exposure, $V_E$ decreased but remained elevated after the initial 23 days of exposure (Schaefer et al. 1963). A similar pattern of increased $V_E$ followed by a return toward baseline occurred in 4 subjects exposed to 1.4% or 0.7% $CO_2$ for 22 days, but because of the small number of subjects, variability during baseline conditions, and higher than expected baseline values, changes failed to reach statistical significance (Elliott et al. 1998). Additionally, subjects demonstrated a reduced ventilatory response to a 5% $CO_2$ challenge during chronic low-level $CO_2$ exposure (Schaefer et al. 1963) and reduced $V_E$ during sustained elevations in $P_{ET}CO_2$ (Elliott et al. 1998). Together, these data suggest the early increase in ventilation during exposure to an elevated $CO_2$ environment becomes blunted as chronic $CO_2$ exposure progresses. However,
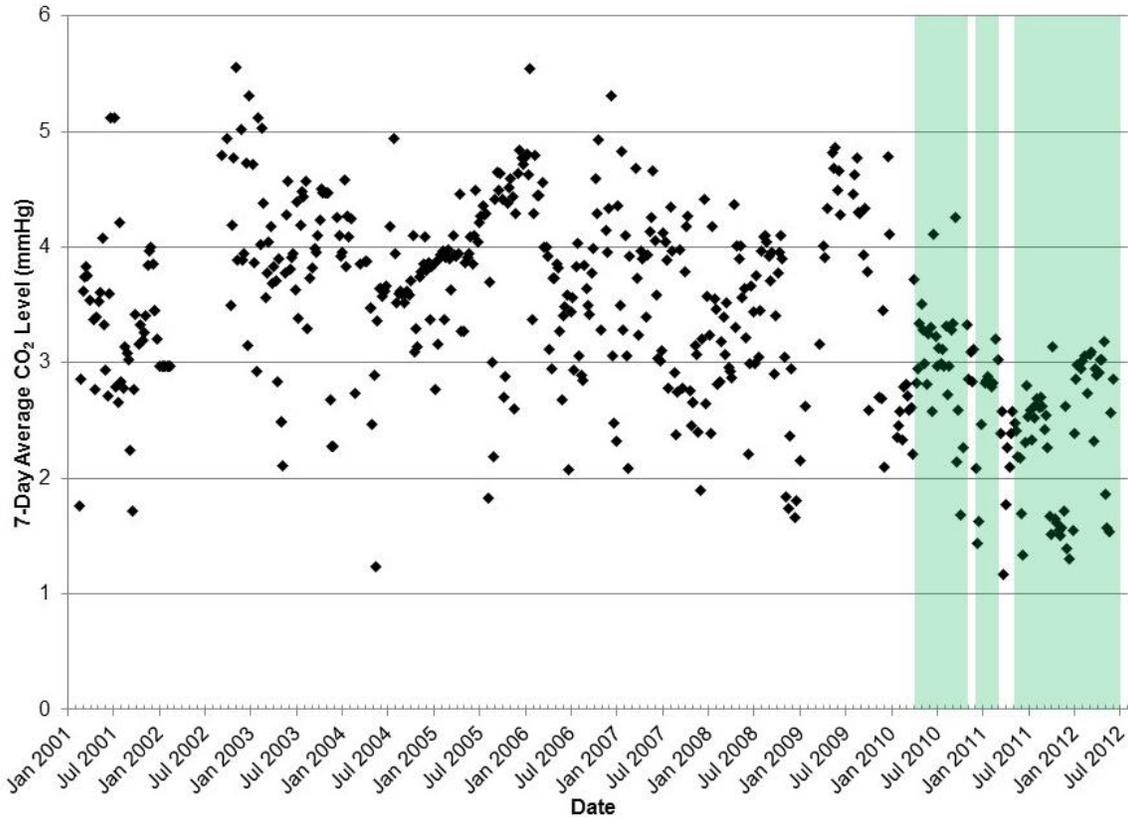
**Figure 28** *Average partial pressure of $CO_2$ in ambient air of the International Space Station. Vertical green bars represent time periods when ambient levels were targeted to remain below 4 mm Hg. Modified from Law et al. JOEM, 56:477-83, 2014.*

the increasing *variability* in arterialized $PCO_2$ measured in these subjects throughout the chronic hypercapnic exposure (Sliwka et al. 1998) suggests variability in acclimatization between individuals. One contributing factor to the variability in ventilatory acclimatization to $CO_2$ may be driven by ventilatory strategy and differences in tidal volume. Those with a high ventilatory response to 5% $CO_2$ before chronic 1.5% $CO_2$ exposure demonstrated a blunted ventilatory response to the 5% $CO_2$ challenge at the conclusion of the 42 day exposure and a respiratory pattern characterized by a higher respiratory rate and lower tidal volume (Schaefer et al. 1963). Conversely, those with a mild ventilatory response to a 5% $CO_2$ challenge demonstrated little change in ventilatory response after chronic $CO_2$ exposure. Thus, while ventilatory response to $CO_2$ appears to be blunted during prolonged $CO_2$ exposures, the response may vary between individuals. Should changes in $CO_2$ sensitivity after chronic $CO_2$ exposure relate to SANS susceptibility, ventilatory response and/or strategy prior to spaceflight may provide an opportunity to predict SANS susceptibility. Whether the variability in ventilatory response to $CO_2$ prior to spaceflight will predict differences in acclimatization to chronic $CO_2$, cerebral vasculature regulation during or after spaceflight, or variability in SANS incidence remains unknown.

Four subjects exposed to 0.7% and 1.2% $CO_2$ for 23 days demonstrated an increase in middle cerebral artery blood flow velocity during the first few days of $CO_2$ exposure, which then decreased yet remained elevated relative to pre-exposure levels (Sliwka et al. 1998). Because only

4 subjects participated in this study, it is unclear if the increasing *variability* in cerebral blood flow velocity that occurred throughout the 23-day exposure resulted from differences in cerebral vascular reactivity or reflected the variability in resulting arterial $PCO_2$. Unexpectedly, the elevated cerebral blood flow remained elevated for up to 5 days after returning to ambient air, suggesting a chronic adaptation to $CO_2$ had in fact occurred. Cerebral blood flow velocity, cerebrovascular reactivity to $CO_2$, and arterial blood gases will be measured before, during, and after 30 days of 6-degree HDT with a 0.5% $CO_2$ environment and conclude data collection in December of 2017. Despite the reduction in cerebrovascular reactivity to $CO_2$ *after* long-duration spaceflight (Zuj et al. 2012), no measures of $CO_2$ sensitivity have been conducted *during* prolonged spaceflight when additional factors may be necessary to impair cerebral autoregulation and contribute to enhanced cerebral vasodilation.

Intracranial pressure has never been measured in humans during chronic exposure to elevated levels of $CO_2$. However, ICP in male Wistar rats exposed to 10% $CO_2$ for 21 weeks was no different from ICP in control animals housed in room air for the same duration ($5.9 \pm 0.4$ vs $5.1 \pm 0.4$ mmHg, respectively) (Kondo et al. 1999). When the control animals were acutely exposed to 10% $CO_2$ ICP increased to 9.9 mmHg, suggesting the chronic exposure led to an acclimatization. Additional experiments within this study pointed toward a blunting of nitric oxide-dependent vasodilation in response to the elevated arterial $PCO_2$ levels for the acute increase and subsequent decrease in ICP with chronic hypercapnic exposure. Research targeted to conclude in 2018 is using the rat hind-limb unloading model to measure ICP and ocular outcomes in various groups of rats, including 1 group exposed to a mild hypercapnic environment

*3. Diet and Sodium*

Sodium, most commonly consumed as dietary sodium chloride (salt) is a required nutrient, used in numerous physiological functions, including the regulation of normal distribution of water between the various compartments of the human body (Scott M. Smith et al. 2015). While the Institute of Medicine and the American Heart Association recommend 1500 mg of sodium per day as an adequate intake level (Appel et al. 2011; Susic and Frohlich 2012), most of the Western world's population consumes a much higher amount; as an example, the average daily sodium intake in the U.S. is more than 3,400 mg (US Dept of Agriculture). Consumption of excessive salt has been linked to numerous adverse health effects, including hypertension, as well as pressure-independent pathologies such as increased risk for stroke, subclinical cardiovascular disease (left ventricular hypertrophy, ventricular fibrosis, diastolic dysfunction, arterial fibrosis leading to large elastic artery stiffness), fibrotic kidney damage, gastric cancer, and disordered mineral metabolism with increased urinary calcium excretion, potentially leading to osteoporosis. The increased non-pressure related fibrosis is due to increased oxidative stress and endothelial dysfunction in the setting of high sodium intake, leading to increased mitogenic responses that translate into fibrosis in the heart, kidneys, and arteries (Appel et al. 2011; Susic and Frohlich 2012). An acute increase in sodium intake has been shown to impair vascular endothelial function in young adults with normal blood pressure (Appel et al. 2011; Susic and Frohlich 2012), and it is has been shown that in middle-aged adults with elevated systolic blood pressure but no other health problems reducing sodium intake from moderate levels to less than 1500 mg/d reduces large elastic artery stiffness (Appel et al. 2011). Sodium reduction decreases

pressure in both normotensive and hypertensive individuals, although the magnitude of this response is still unknown (Appel et al. 2011; Susic and Frohlich 2012).

Foods prepared for spaceflight have always been high in sodium content, a consequence of the food preservation techniques. During the Skylab and Shuttle eras, as well as today in the ISS era, the average amount of sodium intake is 4-5 grams daily, with some individuals reported to consume as much a 7-10 grams daily (Scott M. Smith et al. 2015). Recent efforts at NASA have led to a reduction in the sodium content of many of these food items, leading to daily sodium intake of around 3000 mg/d (Lane et al. 2013).

During real and simulated spaceflight, sodium homeostasis and blood sodium levels are maintained (Scott M. Smith et al. 2015). Over 90% of the dietary sodium in absorbed, so that increased sodium intake leads to an increase in sodium levels in the blood, followed by excretion of the excesses in the urine (Scott M. Smith et al. 2015). The concern with elevated sodium intake in the context of spaceflight is related to its potential impact on bone health and SANS. More specifically for SANS, the concern is that the sodium will contribute to elevation in arterial blood pressure and to non-pressure related elevations in arterial stiffness. In addition, increased sodium intake may induce an expansion of the extracellular fluid volume, which in combination with weightlessness-induced fluid shifts might worsen elevations in intracranial pressure.

A link between increased ICP and altered sodium and water retention was suggested by a study in which 77% of IIH patients had evidence of peripheral edema and 80% had orthostatic retention of sodium and water (Friedman and Streeten 1998). Impaired saline and water load excretions in the upright posture were noted in IIH patients with orthostatic edema as compared values from lean and obese controls without IIH. However, the precise mechanisms linking orthostatic changes and IIH were not defined, and many IIH patients do not have these sodium and water abnormalities. Astronauts are well known to have orthostatic intolerance upon return to gravity after long-duration spaceflight, and the dietary sodium on orbit is also known to be in excess of 5 grams per day in some cases.

## 4. Radiation

The space radiation environment in low Earth orbit, where the ISS is located, exposes astronauts to higher levels of radiation compared to that found on the surface of the Earth, but the Earth's magnetosphere provides substantial protection even in low Earth orbit. However, exploration class missions beyond the protection of Earth's magnetosphere will expose astronauts to greater levels of radiation, in particular galactic cosmic radiation (GCR) (Hassler et al. 2014). Although it is unlikely, crew may also be exposed to higher doses during a solar particle event (SPE).

Very high levels (20 Gy) of radiation exposure are reported to result in brain edema and neuro-inflammation, due to impaired brain-blood barrier (BBB) function (Yuan et al. 2003, 2006; Bellone et al. 2016) and models suggest this may result in elevated intracranial pressure (Lakin et al. 2007). Some mini-pigs exposed to 2.5 Gy electron simulated solar particle event had higher CSF opening pressures 90-days after exposure (Sanzari et al. 2014). Preliminary data from Sprague-Dawley rats fed an iron-rich diet and exposed to 3 Gy spread over 16 days (37.5 cGy per day every other day) showed greater oxidative stress in the retina and aortic vasculature,

suggesting cellular protection mechanisms may be overloaded by the combination of iron load and radiation exposure (Theriot et al. 2016). Published studies that demonstrate radiation induced alteration in blood-brain barrier used radiation doses much higher than those expected to occur during a nominal mission. Therefore, it is unclear if chronic low-dose, low-linear energy transfer (LET) radiation can alter the blood brain or retinal barriers and disrupt cognitive and visual function. In addition, it is unclear if high-LET radiation, the main components of GCR, affects tissues differently than the low-LET radiation typically used in experimental tests on the ground.

## E. Cardiovascular Adaptations

### 1. *Spaceflight-Induced Fluid Shift*

Spaceflight is known to cause a cephalad fluid shift secondary to the loss of the hydrostatic pressure gradient normally experienced on Earth. Moore and Thornton suggest a 2000 mL shift from the legs to the upper body (Moore and Thornton 1987). Ground-based analogs of spaceflight, such as head-out water immersion and HDT bed rest, suggest that the fluid shift is between 700 to 3000 mL (Arborelius et al. 1972; Montgomery 1987; Moore and Thornton 1987). This fluid shift leads to transient increases in stroke volume (Lathers et al. 1989; Liu et al. 2012) and cardiac output (Norsk et al. 2006) and significant variability is likely across astronauts in the type and volume of the fluid shift experienced in spaceflight (Montgomery 1987). While fluid shift seen in bed rest results in a reflex diuresis, the mechanisms of fluid redistribution are far less clear during spaceflight (Leach et al. 1996).

The distribution of fluids in the body is influenced by the direction and magnitude of gravity and the resulting hydrostatic gradients. On Earth, standing up from a supine position in a gravity field imposes a substantial challenge to the human cardiovascular system. Due to the increase in hydrostatic pressure gradient acting along the length of the body, venous volume increases by approximately 500 mL (Rowell 1993). This redistribution of fluid from the central circulation is immediately detected by baroreceptors (pressure) and, in time, by volume (osmolarity) receptors, activating reflex responses to increase heart rate, contractility, and vascular resistance to maintain blood pressure. When astronauts enter the microgravity environment of spaceflight, the opposite effect occurs. It has been well documented that microgravity leads to a cephalad fluid shift in the absence of the hydrostatic pressure gradient (Thornton et al. 1977, 1987; Kas'ian et al. 1980; Moore and Thornton 1987; Kirsch et al. 1993).

One of the first physiologic changes noted during the Apollo program was the decrease in plasma volume, exhibited by the decrease in weight of the crewmen (Leach et al. 1975). It was initially hypothesized that this decrease in plasma volume was a reflex response to a cephalad fluid shift, although the etiology of this plasma volume decrement was never clearly characterized. The time course of the plasma volume losses was unknown due to the lack of in-flight measurements, but the degree of plasma volume loss was independent of the duration of the Apollo mission (Leach et al. 1975).

Later, the cephalad fluid shift upon entry into microgravity was documented using anthropometric measures. Although pre- and postflight anthropometric changes lacked the ability to distinguish between changes in fluid status and tissue loss, it was assumed that the rapid recovery of anthropometric measures after flight represented fluid shifts and plasma volume

recovery; the more gradual recovery was presumed to result from lean tissue and fat mass accretion. Sixteen of 24 Apollo astronauts experienced a mean decrease in calf circumference of 3% immediately after spaceflight that was not fully restored 5 days later, suggesting that the loss was a combination of fluid and muscle atrophy (Hoffler and Johnson 1975).

Anthropometric observations made during the Skylab 2 and 3 missions demonstrated a decrease in thigh circumference, suggesting that these astronauts experienced a significant fluid shift and muscle atrophy during the course of their missions. More extensive circumferential measures were obtained during Skylab 4 (Thornton et al. 1977), when it was found that astronauts experience a rapid loss in leg volume early during their flight, too rapid to be explained by fat or lean tissue loss, but the change was consistent with the cephalic fluid shift that occurs during spaceflight. These measures were performed every 3 cm along the leg and the arm, around the neck, chest, abdomen, and hip (Figure 29).
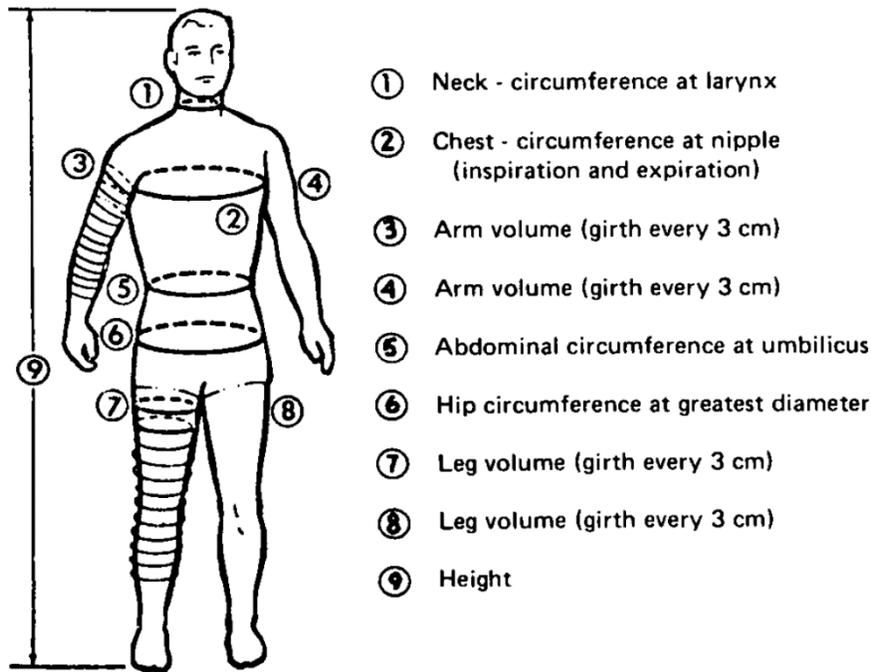


**Figure 29** Circumference measures used to calculate volume of fluid shift during Skylab 4.

Interestingly, there was little to no change in arm volume in these subjects from before to during flight and from during to after flight, suggesting that neither arm fluid volume nor tissue volume changed during the course of their mission (Figure 30). Furthermore, lower limb veins were not distended, whereas the veins of the upper body, including the jugular, temple and forehead veins were completely full and distended. It was hypothesized that intra and extravascular fluid shifts to above heart level had occurred and that increased transmural pressure led to cephalad edema (puffy face).
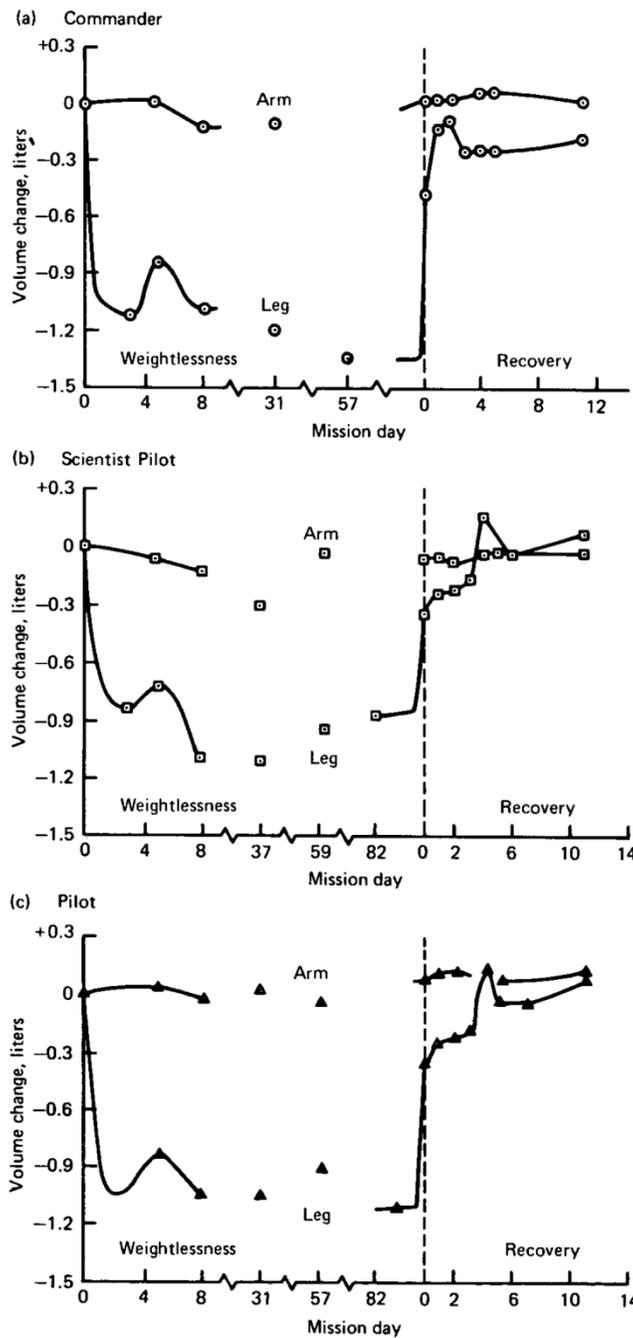
**Figure 30** Volume changes pre, in, and postflight from Skylab 4.

Anthropometric measurements of the thigh and calf also were obtained using stocking plethysmography in 11 astronauts during and after 5 early Shuttle flights (STS-7, 8, 51D, 51B, 61B) (Thornton et al. 1977; Moore and Thornton 1987) (Figure 31). As expected, upon entry into microgravity, leg volume decreased by 12% and was believed to result from a rapid shift in fluid volume to the upper body, with confirmatory evidence in the form of photographs of puffy faces as well as reports of nasal congestion and "full headedness". The total fluid shift was reported to

69

be 2 L, 1 L from each leg, with the majority of the volume coming from the thigh. Most of this fluid shift occurred in the first 6 to 10 hours after entering microgravity, followed by a subsequent slow negative decline or plateau. Similar to observations after Skylab missions, when measurements were repeated within 1.5 hours of landing while the astronauts were standing, the difference between pre and postflight leg volume was less than the measured loss during flight, amounting to only an average decrease in leg volume of 4%. The decreased volume upon landing was likely the combined result of lower plasma volume, decreased fat mass, and lower muscle mass. One week after Shuttle landing, leg volume still was 3% lower than before flight although plasma volume would have been recovered by this time. Using a similar method, Kas'ian *et al.* (Kas'ian et al. 1980) reported a decrease in leg volume of 6% to 7% within the first week of flight in 2 cosmonauts, which progressively decreased to 18% to 23% reduced leg volume by flight day 120 of the Salyut-6 mission. The absence of postflight tests makes interpretation of these volume changes difficult, as it is unclear how much of the volume loss was due to muscle atrophy.
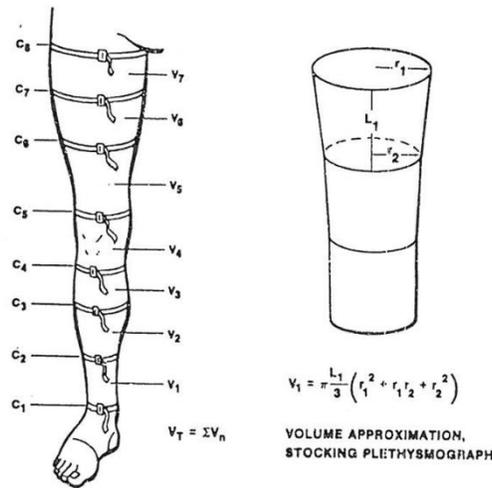


**Figure 31** *Schematic of leg plethysmograph and Dr. William Thornton making measurements on Commander Richard Truly on STS-8. Reproduced from Moore TP, et al. with permission of the Aerospace Medical Association.*

Kirsch *et al.* (Kirsch et al. 1993) used A-mode ultrasound to measure the spaceflight-induced fluid shift in one cosmonaut on the Mir 1992 mission using interstitial thickness measures over the forehead and tibia. Measurements were obtained before flight (supine and head-down), 8 times during flight, and 7 days after the flight. Facial tissues swelled during the first 3 days of the mission. Tibial interstitial thickness was 20% less than before flight and remained low for the duration of the flight and immediately upon landing. Body weight did not fully recover within the first 4 days after landing, suggesting that only a portion of the interstitial thickness changes were fluid dependent.

2. *Plasma Volume Losses*

It is well documented that plasma volume decreases with spaceflight (Johnson et al. 1977; Leach et al. 1996; Buckey et al. 1996b; Waters et al. 2002) although the exact mechanism of this plasma volume decrease is not completely understood. Red cell mass is decreased in spaceflight (Johnson et al. 1977; Udden et al. 1995; Alfrey et al. 1996) appropriately as a reflex

response to hemoconcentration after reduced plasma volume. Leach and coworkers initially reported that total body water is decreased after short-duration Shuttle flights (Leach et al. 1991), yet suggested that this may have been exaggerated by a space motion sickness-induced reduction in water intake. Several years later, they published the results of SLS-1 and SLS-2 studies in which they measured plasma volume, total body water, and extra and intracellular fluid volumes in 7 astronauts. In this report, Leach and coworkers reported that plasma and extracellular fluid volume were decreased, whereas total body water was unchanged, suggesting that the intracellular fluid volume was increased. This reduction occurred despite no report of natriuresis or diuresis, similar to results from Drummer *et al.* (Drummer et al. 1993). It is generally accepted that diuresis is not the cause of reduced plasma volume during spaceflight, but rather a combination of decreased water balance (i.e., reduced intake) and extravasation into intracellular and interstitial compartments (Norsk 2005). Leach *et al.* (Leach et al. 1996) reported a negative water balance and reduced total circulating protein in the astronauts. They suggested that a rapid filtration of protein out of the vascular space is responsible for the early plasma volume loss and a negative water balance perpetuates this hypovolemia. Norsk also reported a negative water balance during spaceflight, which is more pronounced than during bed rest (Norsk 2000).

*3. Central Venous Pressure (CVP)*

In the early days of the Shuttle era, the spaceflight-induced cephalad fluid shift was well-known and assumed to cause an increase in CVP. Norsk *et al.* (Norsk et al. 1987) measured CVP in 14 subjects while seated upright during parabolic flight and determined only a slight (1.8 mmHg) increase in CVP during short periods of weightlessness. When 7 subjects were studied in a separate parabolic flight study in which CVP was measured in the supine posture, Foldager and coworkers reported a decrease from $6.5 \pm 1.3$ during 1*g* to $5.0 \pm 1.3$ mmHg during weightlessness (Foldager et al. 1996). They were also able to measure CVP in one Spacelab D-2 astronaut, and concluded that CVP in microgravity is close to or below measured values in 1-G supine position. Earlier, Kirsch and co-workers measured peripheral venous pressure in 4 Spacelab-1 astronauts and suggested that these measures would be analogous to central venous pressure (Kirsch et al. 1984). All 4 astronauts were reported to have reductions in venous pressure measures; however, only data for 2 of the astronauts were reported. One astronaut was reported to experience a reduction in CVP, assumed to be equivalent to venous pressure measured peripherally, from 9.5 cm $H_2O$ (7 mmHg) on the day before flight to 6.5 and 2.6 cm $H_2O$ (4.8 and 2 mmHg) on the first and sixth days of flight, respectively. CVP in a second astronaut was reduced from 15.2 cm $H_2O$ (11.2 mmHg) on the day before flight to 6.5 and 7.7 cm $H_2O$ (4.8 and 5.7 mmHg) on days 1 and 6 of flight, respectively (Kirsch et al. 1984). These findings were supported by two separate studies by Buckey et al. (Buckey et al. 1993, 1996a). The first report was from a Spacelab Life Sciences (SLS-1) flight in which CVP was measured before flight while seated and while in the launch position in the orbiter, during launch, and during the initial moments upon reaching microgravity. CVP increased from 5 to 6 cm $H_2O$ (3.7 to 4.4 mmHg) while seated to 10 to 12 cm $H_2O$ (7.4 to 8.8 mmHg) in the launch position. It increased further during the launch, presumably from the $G_x$ forces, to 15 to 17 cm $H_2O$ (11 to 12.5 mmHg) before decreasing to 0 to minus 3 cm $H_2O$ (0 to minus 2.2 mmHg) upon entering microgravity (Figure 32). This reduction was rapid, occurring during the first minute of entering microgravity, and remained within 1 to 2 cm $H_2O$ (0.7 to 1.4 mmHg) until the catheter was removed (Buckey et al. 1993). Interestingly, heart size in this astronaut increased at the same time that CVP decreased. Similar results were obtained in a second report of 2 SLS-2

crewmembers (Buckey et al. 1996a). Mean CVP (2 SLS-2 crewmembers and 1 SLS-1 crewmember) increased from 8.4 cm $H_2O$ (6.2 mmHg) before flight to 15 cm $H_2O$ (11 mmHg) in the launch position, to 2.5 cm $H_2O$ (1.8 mmHg) after 10 minutes in microgravity. Cardiac filling was increased, despite the reduction in CVP, suggesting that effective filling pressure was elevated due to the reduced transmural pressure applied from the lungs and abdominal organs in weightlessness.
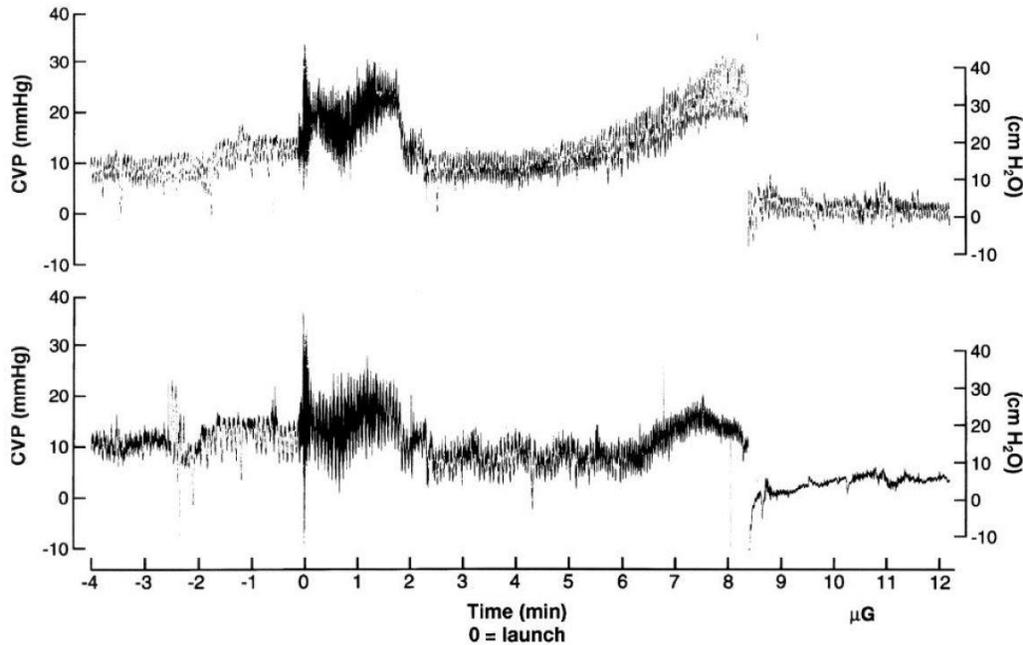


**Figure 32** *CVP tracing from two SLS-2 astronauts showing the decrease in CVP upon exposure to microgravity 8.5 minutes post-launch. Reproduced from Buckey JC Jr, et al. with permission from The American Physiological Society, obtained via Copyright Clearance Center, Inc.*

Videbaek and coworkers tested this hypothesis by measuring central venous pressure, esophageal pressure (EP – a surrogate of intrathoracic pressure) and atrial distension in 7 men during parabolic flight (Videbaek and Norsk 1997). The CVP during the microgravity period of parabolic flight decreased from $5.8 \pm 1.5$ to $4.5 \pm 1.1$ mmHg and esophageal pressure decreased from $1.5 \pm 1.6$ to $-4.1 \pm 1.7$ mmHg. Left atrial diameter increased from $26.8 \pm 1.2$ mm to $30.4 \pm 0.7$ mm. Despite the decrease in CVP, the left atrial filling pressure was elevated (as demonstrated by left atrial distension). Videbaek suggests that the difference in CVP and EP results in an increased transmural central venous pressure, which explains the increased cardiac filling despite the reduced CVP. Furthermore, they report increased left ventricular end diastolic volume, stroke volume, and cardiac output, likely the result of the chest wall changing shape and expanding in the absence of gravity. White and Blomqvist used a 3-compartment cardiovascular model to simulate the relaxation of the chest in microgravity (White and Blomqvist 1998). Their results indicate that relaxation of the chest would increase the transmural filling pressure of the heart, increase left ventricular end diastolic volume, stroke volume, and cardiac output, similar to

the results obtained by Videbaek in parabolic flight. Prisk *et al.* (Prisk et al. 1993) also reported elevated stroke volume and cardiac output in 4 SLS-1 astronauts.

*4. Transcapillary Fluid Pressure*

Kirsch *et al.* (Kirsch et al. 1993) were one of the first to clearly show interstitial swelling in the forehead during flight, which supports the many anecdotal reports of puffy faces, sinus congestion, and feeling of a full head during spaceflight. However, little evidence exists of filtration into the extravascular space in the head and neck during spaceflight. Using a ground-based analog of 10-degree HDT, Diridollou and coworkers (Diridollou et al. 2000), showed that after 24 hours subjects presented with forehead interstitial swelling similar to that seen by Kirsch (Kirsch et al. 1993). Linnarsson *et al.* (Linnarsson et al. 1985) used tetrapolar bioimpedance to measure segmental fluid shifts during 7-degree HDT bed rest. The authors suggest that the initial interstitial swelling is a result of a rapid blood shift, which is detected as a plasma volume expansion and is followed by a more gradual extravascular shift from the legs over the course of 2 hours. Bioimpedance detected extravascular volume leaving the thigh and the calf, but not entering the chest, suggesting that this volume was being absorbed into the vascular space. This would result in a transient decrease in plasma oncotic pressure. This is supported by a study by Hsieh *et al.* (Hsieh et al. 1998) who reported an initial decreased oncotic pressure in the time frame reported by Linnarsson (Linnarsson et al. 1985), but this ultimately resulted in an elevated colloid osmotic pressure. Similarly, Parazynski *et al.* (Parazynski et al. 1991) reported an initial decrease in colloid oncotic pressure from $21.5 \pm 1.5$ mmHg to $18.1 \pm 1.9$ mmHg within the first 4 hours of HDT. They suggest that this decrease in plasma oncotic pressure is a result of the change from filtration to absorption in the capillary beds below the heart. This colloid oncotic pressure is thought to gradually return to baseline and is described by the Starling-Landis equation

The Starling-Landis equation describes fluid movement in the microvasculature:

$$J_v = K_f[(P_c - P_i) - \sigma(\pi_c - \pi_i)]$$

$J_v = Net\ fluid\ movement$
$K_f = Filtration\ coefficient$
$P_c = Capillary\ fluid\ pressure$
$P_i = Interstitial\ fluid\ pressure$
$\sigma = Reflection\ coefficient$
$\pi_c = Capillary\ oncotic\ pressure$
$\pi_i = Interstitial\ oncotic\ pressure$

Fluid movement into or out of the capillaries is dependent on the hydrostatic pressure drop ($P_c - P_i$) minus the colloid osmotic pressure drop ($\pi_c - \pi_i$). The filtration coefficient ($K_f$) takes into account the permeability of the capillary membranes to water, which is dependent on surface area and hydrostatic conductance. The reflection coefficient ($\sigma$) is used to correct for the fact that not all plasma proteins are effective in retaining water, and is different in various vascular beds.

Parazynski *et al.*, were the first to quantify all 4 Starling-Landis pressures during HDT (Parazynski et al. 1991). They measured upper body capillary and interstitial fluid pressures, as well as plasma and tissue oncotic pressures in 7 men during 8 hours of 6-degree HDT. Capillary fluid pressure increased from $27.7 \pm 1.5$ mmHg to $33.9 \pm 1.7$ mmHg at the end of bed rest, while interstitial fluid pressure did not change significantly (Figure 33). Although plasma oncotic pressure initially decreased, it returned to baseline by the end of 8 hours of bed rest. Subcutaneous and intramuscular colloid osmotic pressure in the face and neck did not change. Parazynski and coworkers suggest that the significantly elevated net Transcapillary pressure gradient in the head and neck is the reason for cephalic edema during bed rest and spaceflight. They further suggest that capillaries above the heart may be more permeable to protein filtration than those below the heart, similar to the results by Leach *et al.* (Leach et al. 1996). Hargens measured interstitial pressure in the lower leg muscles and subcutaneous tissues and reported a decrease in tissue pressure of 7.4 and 4.4 mmHg, respectively (Hargens 1983). He also hypothesized that lower leg vascular absorption results in decreased vascular oncotic pressure and, coupled with increased cephalic capillary pressure, results in filtration in the upper body. Several years later, in a separate review, Hargens further postulated that the reduced tissue weight in microgravity results in lower interstitial fluid pressure, further shifting the Starling balance to net filtration during spaceflight (Hargens and Watenpaugh 1996).
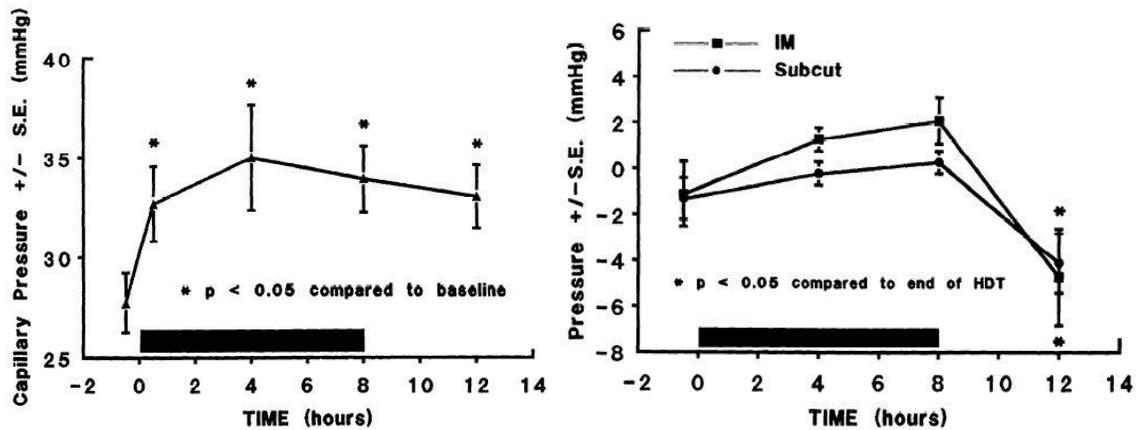


**Figure 33** Capillary (left) and interstitial fluid pressure (right) during 8 hours of HDT bed rest. Capillary pressure is significantly elevated and interstitial fluid pressure does not significantly change. Reproduced from Parazynski *et al.* with permission from The American Physiological Society, obtained via Copyright Clearance Center, Inc.

Cephalad edema may be further exacerbated in spaceflight by changes in microvascular water permeability. In a lumped parameter cardiovascular model, Lakin *et al.* (Lakin et al. 2007) postulated that cerebral fluid filtration is increased if the space between endothelial cells of the cerebral blood vessels is increased. This would be possible in spaceflight if the gravity-induced hydrostatic pressure gradients in the cerebral interstitium were removed. They also suggest that radiation exposure during spaceflight may alter endothelial protein structure such that cells shrink, increasing permeability between cell junctions. Christ *et al.* (Christ et al. 2001) showed that fluid filtration capacity (capillary permeability) is increased during long-duration bed rest, and this may be enhance in the presence of free $O_2$ radicals and activated leukocytes, such as during exposure to spaceflight radiation and other oxidative stressors.

Diedrich *et al.* (Diedrich et al. 2007) summarizes the current model of spaceflight-induced fluid volume changes (Figure 34). Exposure to microgravity causes a cephalad fluid shift secondary to the removal of the hydrostatic pressure gradient. CVP is reduced due to expansion of the chest and decreased pressure from tissue and organs. This reduction in tissue compression likely plays a role in extravasation of fluid, resulting in overall reduced plasma volume and cephalic edema.
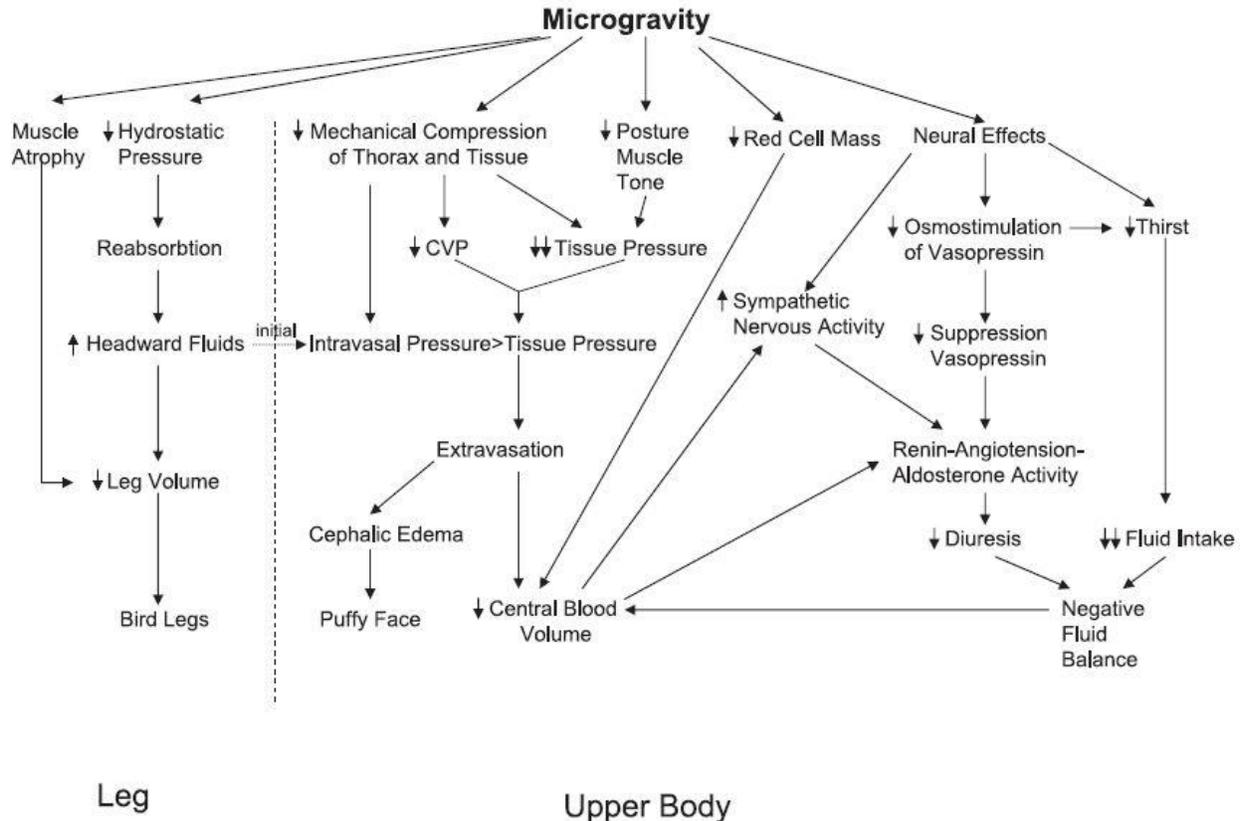


**Figure 34** Flow diagram of predicted blood and fluid volume changes during spaceflight. Reproduced from Diedrich A, et al. with permission of Wolters Kluwer Health, obtained via RightsLink.

### 5. *Arterial and Venous Resistance*

Brief exposures to weightlessness during parabolic flight induces increased cardiac dimensions, cardiac output, and stroke volume (Caiani et al. 2006). Elevated cardiac output and stroke volume persist during short-duration space flight; the highest values are recorded early in the mission but still remaining above preflight standing values after a week of weightlessness (Prisk et al. 1993). Furthermore, Norsk *et al.* (Norsk et al. 2015) reported an increased cardiac output and decreased vascular resistance during 24 h recordings of 8 male astronauts on the ISS ISS after 3 to 6 months of spaceflight. Despite no significant change in common carotid artery and femoral artery diameter during 4 to 6 months of spaceflight, common carotid artery flow increased during the first month, but decreased to preflight levels by 3 to 6 months of spaceflight. However, there was no change in femoral artery flow (Arbeille et al. 2001).

Given the distensibility of the veins, changes in hydrostatic pressures during HDT bed rest and spaceflight are expected to result in changes in venous dimensions. While HDT results in jugular vein distension and smaller femoral vein area (Arbeille et al. 2001), this is not the case in spaceflight. Herault *et al.* (Herault et al. 2000) and Arbeille *et al.* (Arbeille et al. 2001) reported significant engorgement of the jugular and femoral veins during spaceflight and veins remained distended by as much as 40% after 6 months of spaceflight (Figure 35).
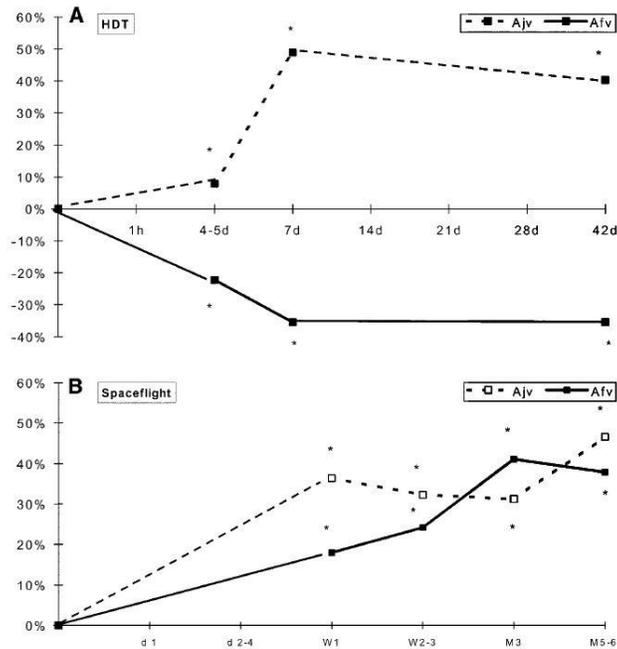


**Figure 35** *Divergent vein diameter responses between HDT bed rest (panel A) and spaceflight (panel B). The panels show percentage change of the preflight values, measured at 1h, and days 4-5, 7, 15, 21, 28 and 42 during HDT, and at days 1 and 2-4, weeks 1 and 2-3, and months 3 and 5-6 during spaceflight. The jugular vein is distended in both real and simulated microgravity, while the femoral vein is only distended in real microgravity. $A_{jv}$ - Jugular vein cross-sectional area. $A_{fv}$ - Femoral vein cross sectional area. * $P<0.05$, significantly different from preflight or pre-HDT values. Reproduced from Arbeille P, and others with permission of Springer-Verlag, obtained via Copyright Clearance Center, Inc.*

Jugular vein distension upon entry into weightlessness may result from either increased venous pressure or increased transmural pressure. While increased transmural pressure plays a role in atrial filling during weightlessness, the weight of the tissue overlying the jugular vein likely is small in comparison. Recently, Martin *et al.* (Martin et al. 2016) reported that venous pressure measured non-invasively in the internal jugular vein, the primary vein draining the cranium, is elevated during parabolic flight to levels similar to those observed during 20 degree HDT. While limitations to the measurement technique (compression sonography) and the model (parabolic flight) exist, these data in combination with distended jugular vein dimensions are suggestive of venous congestion in the head and upper torso secondary to the cephalad fluid shift. Brief exposures to reduced gravity by free fall and parabolic flight also have been reported to increase jugular vein pressures in rats (Gotoh et al. 2004; Tanaka et al. 2005). Whether this acute response of jugular vein pressure plays a role in jugular vein distension and ocular structural changes during prolonged weightlessness has yet to be tested.

*6. Vascular Adaptations to Spaceflight*

Normal blood vessel function is necessary for sustaining and adapting to the metabolic demands of individual organs. To meet the blood flow requirements of organs and local tissue beds, arteries and veins must be able to respond rapidly to diverse physical and chemical signals by changing either vessel caliber (diameter) or altering the density of the vascular network. Several factors regulate how vessels respond to modifications in demand including humoral, neural, and autoregulatory. Importantly, changes to any of these systems such as in response to chronic activation from environmental stimuli or injury may result in impaired vascular control and contribute to numerous pathologies.

Medical data from as early as the Mercury and Gemini missions indicate that exposure to microgravity results in cardiovascular deconditioning that presents as orthostatic intolerance upon return to Earth's gravity (Berry 1968). While many researchers agree that the space-related deconditioning is likely triggered by a headward fluid shift and a reduced plasma volume, a preponderance of evidence indicates that the loss of vascular control, indicated by lower peripheral resistance and increased blood pooling in the lower limbs, is a primary mechanism for postflight orthostatic hypotension and is independent of volume status (Blomqvist et al. 1994; Buckey et al. 1996b; Fritsch-Yelle et al. 1996; Baisch et al. 2000; Watenpaugh et al. 2001; Waters et al. 2002). For example, flight data from both Buckey (Buckey et al. 1996b) and Fritsch-Yelle *et al.* (Fritsch-Yelle et al. 1996) demonstrated that astronauts who finished a postflight stand test, compared to those who became presyncopal, had a significantly greater vasoconstrictor response with higher total peripheral resistance. Fritsch-Yelle *et al.* suggested that the lower level of peripheral resistance, associated with an increased incidence of postflight orthostatic hypotension, is likely due to a smaller postflight increase in circulating levels of norepinephrine and is less likely related to volume status as there were no differences in plasma volume levels between presyncopal and nonpresyncopal subjects. Ground-based studies using HDT bed rest to simulate microgravity overwhelmingly confirm a significant relation between orthostatic intolerance and a decreased vasoconstrictor response that is evidenced by increased lower limb venous compliance (Convertino et al. 1989; Buckey et al. 1990, 1992; Bleeker et al. 2004).

Along similar lines of thought, differences between astronauts who become presyncopal and those that are nonpresyncopal on landing day may provide additional insight into the effects of spaceflight that might contribute to in-flight vision changes. Specifically, Tuday *et al.* (Tuday et al. 2007) observed that although vascular compliance, calculated as stroke volume divided by pulse pressure, was not different between the astronaut groups before flight, vascular compliance was lower in the nonpresyncopal astronauts than in the presyncopal astronauts on landing day. Perhaps increased stiffness may reflect remodeling of the vascular wall, including increased collagen: elastin ratio, collagen cross-linking, and modifications of the vascular matrix. Although this response to spaceflight may be to protect against postflight orthostatic intolerance, assuming that the decrease in vascular compliance is similar across all vessels in the body, then perhaps these observed changes may be suggestive of changes in the cerebrovasculature. However, using the hind-limb suspension model in rats, Tuday *et al.* (Tuday et al. 2007) provided some of the first ground-based experimental evidence demonstrating that a reduction in large artery hydrostatic forces results in greater vessel distention and is accompanied by an impaired vasoconstrictor response to the sympathetic neurotransmitter norepinephrine. Since then,

considerable attention has been focused on understanding the mechanisms that underlie many of the microgravity-induced vascular adaptations in relation to orthostatic intolerance. Much of this data has recently been reviewed in-depth by Zhang, who reported that changes in arterial compliance were a local effect resulting from regional changes in blood pressures. A number of other probable explanations may include, a reduced adrenergic receptor sensitivity (Waters et al. 2005), less vasoconstrictor reserve (Convertino 1999; Fu et al. 2004), and an enhanced flow-dependent vasodilator response (Bonnin et al. 2001).

The effects of sex on postflight orthostatic tolerance, or the ability to regulate blood pressure during standing or upright tilt, may be of interest in the investigation of SANS as men appear better able to maintain blood pressure during orthostatic challenges than women, and men also seem to be more susceptible to vision changes during long-duration spaceflight. However, as noted by Fritsch-Yelle *et al.* (Fritsch-Yelle et al. 1996), differences in postflight orthostatic tolerance in the astronaut population may be the result of selection bias. That is, the large majority of astronauts who did not experience orthostatic intolerance on landing day were career military pilots or had high performance aircraft training (Fritsch-Yelle et al. 1996; Lee et al. 1999). To further illustrate this potential bias, the study with the highest incidence of orthostatic intolerance also has the highest proportion of payload specialists (Buckey et al. 1996b).

Recently, 2 studies in ISS astronauts demonstrated local structural and functional changes in the carotid artery in response to 4 to 6 months of spaceflight. First, Arbeille *et al.* (Arbeille et al. 2015) observed that carotid artery intima-media thickness increased ~12% in 8 astronauts (2 women) by the end of their mission, with significantly increased thickness observed as early as 2 weeks after launch. It was presumed that these results were not an artifact of measurements conducted in space by non-experts (astronauts) because the increased carotid intima-media thickness persisted when measurements were repeated by the investigators ~4 days after landing. Similarly intima-media thickness increased in the femoral artery during the spaceflight in these subjects, although there was no pre- to postflight thickening observed after landing. Similar results were obtained from 6 participants of the MARS 500 mission; intima-media thickening in the carotid and femoral arteries increased although the subjects were not exposed to weightlessness (Arbeille et al. 2014), suggesting that other factors such as increased oxidative stress and altered glucose metabolism may play a significant role in these spaceflight-induced structural adaptations. At this time, however, it is not possible to discern the nature of the increase intima-media thickness in humans from sonographic measures used to measure carotid intima-media thickness, although data from Zhang *et al.* (Zhang et al. 1996) and Mao *et al.* (Mao et al. 1999) in rats during hindlimb suspension are suggestive of smooth muscle hyperplasia. Although this thickening in rats is reversible after cessation of hindlimb suspension, there currently are no such recovery measures in astronauts.

Along with carotid artery structural adaptations, there appear to be corresponding changes in carotid artery function. Hughson *et al.* (Hughson et al. 2016a) reported that carotid stiffness was increased and distensibility decreased from before to after flight in 8 astronauts (4 men, 4 women) after 6-month ISS missions. Additionally, pulse wave transit times were decreased, as measured by the time from the R-wave to onset of pressure wave in the foot and in the ankle. These data are suggestive of local adaptations in neck and torso as well as systemic effects. Similarly, arterial compliance, calculated from the ratio of resting stroke volume divided

by pulse pressure, had been previously reported by Tuday *et al.* (Tuday et al. 2007) to decrease on landing day after Space Shuttle missions. While biomarkers of oxidative stress and inflammation were not consistently affected from before to after flight in ISS astronauts, resting insulin, glycalated albumin, and a calculated index of insulin resistance (Homeostatic model assessment, HOMA) were elevated after landing (Hughson et al. 2016a). Functional changes may result from the structural adaptations described previously, but the impact of the neuro-humoral environment in the postflight period, including changes in sympathetic and parasympathetic control, may also be a contributing factor (Baevsky et al. 2007; Hughson et al. 2012).

## 7.  Radiation Effects on Vascular Function

Our present level of knowledge of the vascular effects of radiation, in particular space-like radiation, greatly lags behind that of the microgravity-related vascular alterations. Until recently, the majority of evidence suggesting radiation-induced changes in vascular function was substantiated only by epidemiologic studies such as those reporting data on cardiovascular disease rates in the Hiroshima/Nagasaki atomic bomb survivors (Preston et al. 2003) or the similar findings from the Chernobyl emergency workers (Ivanov et al. 2001). The vascular effects of exposure to radiation are generally focused around cardiovascular disease progression, most notably atherothrombotic vascular disease. Radiation is thought to produce damaging cellular effects either directly (Menendez et al. 1998; Kolesnick and Fuks 2003; Tishkin et al. 2007) or indirectly (Bourlier et al. 1998; Soloviev et al. 2003; Soucy et al. 2007; Simone et al. 2009). Several studies suggest that exposure to radiation impairs endothelial function, shifting the regulatory balance towards increased vasoconstriction through impairment in the nitric oxide pathway (Suvorava et al. 2006; Soucy et al. 2007, 2009). Although a healthy endothelium is primarily associated with maintaining normal vascular function through the production and secretion of several vasoactive substances such as nitric oxide, the endothelium is also a selective permeable barrier that regulates the exchange of fluids and blood constituents (such as plasma proteins and cells) between the circulation and the surrounding tissues. The impaired trafficking of substances from the intravascular space to the extracellular region could have significant implications on the delivery of nutrients and fluid distribution to surrounding tissues and organs. In addition, questions remain as to whether the vascular effects of exposure to microgravity and space-like radiation will be additive, contributing to an even greater pathogenesis, or whether the increase in vascular compliance resulting from the microgravity-induced deconditioning will be offset by the increase in vasoconstrictor tone due to impairment in the nitric oxide pathway.

## 8.  Cerebral and Ocular Circulation

Although it is often overlooked, decrease in cerebral perfusion is critically important in the development of orthostatic intolerance. In general, cerebral blood flow is well protected against systemic changes in pressure or flow without compromising the high demands of brain tissue. However, with a reduction in central volume from both a decrease in plasma volume and blood pooling in the lower limbs, it is reasonable to assume that cerebral blood flow may be impacted after spaceflight.

Blood flow to the brain is supplied by the 2 carotid and 2 vertebral arteries that communicate with each other through the arterial anastomoses that form the circle of Willis.

Under normal conditions the circle of Willis acts only to communicate need and not as a central station where supply is mixed and then delivered to the smaller collateral circulations (Hodes et al. 1947; Wellens et al. 1975). Three pairs of arteries form the circle of Willis and feed specific regions of the brain, the anterior, middle, and posterior cerebral arteries. Extending beyond the larger arteries are dense networks of capillaries where nutrient exchange takes place with a 2 to 3 fold greater density in the gray compared with white matter. The blood is collected and drained by 2 systems of veins, including the deep venous system within the brain and the internal jugular and other veins outside of the skull. Circulation within the skull is unique in that it is tightly regulated by the blood-brain barrier and is therefore protected against ionic and humoral factors. The cerebral vasculature undergoes fine adjustments primarily through autoregulatory processes such that under normal healthy conditions on Earth the cerebral blood vessels have an intrinsic ability to keep blood flow constant over a wide range of arterial blood pressure levels via myogenic, metabolic, and tissue pressure mechanisms.

Data indicate that upon entry into space, the mean arterial pressure in the head increases from approximately 70 mm Hg to 100 mm Hg. The higher cerebral perfusion pressure in turn leads to elevations in both cerebral artery and capillary blood flow, which contribute to elevations in ICP (Hargens and Watenpaugh 1996). It is widely believed that the product of these microgravity-induced alterations in perfusion pressures and blood flow and elevations in ICP contribute over time to pronounced changes in cerebral responsiveness (Buckey et al. 1996b). However, a number of studies suggest that cerebral blood flow is lower in response to spaceflight and head-down bed rest (Kawai et al. 1993; Bassett et al. 1993; Fritsch-Yelle et al. 1996). Specifically, Kawai *et al.* (Kawai et al. 1993) demonstrated that after 24 hours of HDT bed rest peak cerebral blood flow velocity was significantly lower compared to before HDT and remained lower up to 6 hours after HDT (Figure 36). These differences in the literature highlight the need for additional research in this area.
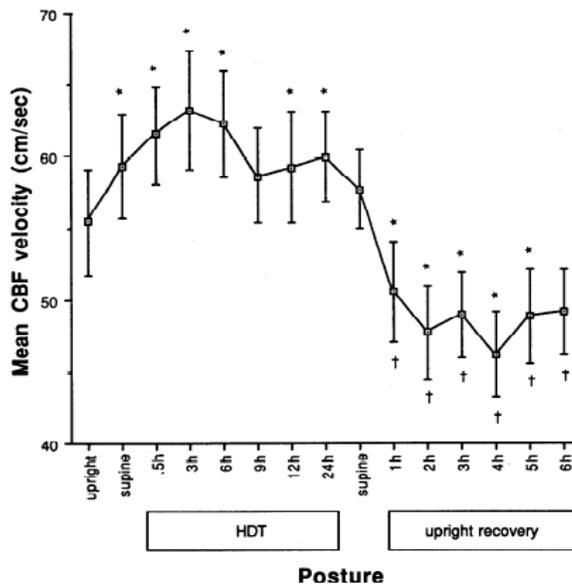


**Figure 36** *The time course of mean cerebral blood flow velocity in subjects after 24-hours HDT bed rest. Reproduced from Kawai Y, et al. with permission from The American Physiological Society, obtained via Copyright Clearance Center, Inc.*

Controversy exists as to whether regulation of blood flow is altered in response to stress (such as, moving from a supine to a standing position), or whether lower blood flow is simply a factor of hypovolemia. Data from Fritsch-Yelle *et al.* (Fritsch-Yelle et al. 1996) do not support a change in regulation; blood flow velocity was measured in the middle cerebral artery using ultrasound and no difference was found in tilt response between presyncopal and nonpresyncopal astronauts. In another study that measured cerebral blood flow, velocities, and beat-to-beat changes in arterial pressure, static autoregulation was not impaired after 16 days in space and, moreover, dynamic regulation (changes occurring during stress) was actually improved (Iwasaki et al. 2007). Interestingly, Greaves *et al.* (Greaves et al. 2007) also reported improved autoregulation in a set of subjects who participated in 60 days of HDT bed rest. Taken together, these data and recent findings from Jeong and colleagues (Jeong et al. 2012) suggest that autoregulation is in fact not impaired and that the alterations in blood flow after spaceflight are related to volume status.

Recent work using phase-contrast MRI demonstrated that total blood flow through the internal carotid and vertebral arteries decreased after 4.5 hours of 6°, 12°, and 18° HDT compared to supine levels (Marshall-Goebel et al. 2016). At 12° HDT internal jugular venous area increased and outflow decreased, suggesting increased venous resistance. The addition of 1% $CO_2$ to the inspired air increased both arterial inflow and venous outflow.

Evidence from several ground-based studies using the rat hind-limb tail suspension model suggests that the reduction in cerebral blood flow is associated with a decrease in autoregulation caused by alterations in cerebral arterial structure and function. Indeed, data from Geary *et al.* (Geary et al. 1998) and Wilkerson *et al.* (Wilkerson et al. 2002, 2005) indicate that myogenic tone and vascular resistance is increased during hind-limb suspension, and that the difference in tone (suspended versus control rats) is related to changes in nitric-oxide-mediated vasodilation. Interestingly, the overall functional consequence of increased tone appears to lead to reduced blood flow, and the stimulus does not appear to be an increase in arterial pressure but rather increases in transmural pressure caused by the elevation in the extravascular pressure in the cranium (Wilkerson et al. 2002).

However, as noted previously, data from similar investigations on cerebral autoregulation in humans during spaceflight do not corroborate the findings in the ground-based analogs. This lack of corroboration between spaceflight and ground-based analogs is in line with evidence from modeling steady-state ICP differences between HDT bed rest and long-duration microgravity exposure (Stevens et al. 2005). It was concluded that ICP should be less in crew exposed to actual microgravity compared to subjects in long-term HDT (Stevens et al. 2005). The reason for the profound differences in findings for spaceflight and ground analogs of spaceflight remains unclear; however, it has been speculated that the central volume shift in fluid, and subsequent redistribution of fluid between compartments and tissues is not comparable in these two conditions.

## 9. *Lymphatics*

Well-regulated lymph function is critical for maintaining normal tissue fluid volume and pressure. The lymphatic system collects excess interstitial fluid and transports this fluid back to the blood through the thoracic duct (Koh et al. 2005). Distal to the thoracic duct, lymph is

pumped against gravity; however, proximal to the duct lymph drains by the aide of gravity. Typically, 8 to 12 liters of interstitial fluid are produced daily by transcapillary fluid filtration and transported through the lymphatic vasculature.

Cervical lymphatics in the nasal submucosa at the cribriform plate can absorb cerebrospinal fluid (Boulton et al. 1999; Johnston 2003; Koh et al. 2005). In addition, lymphatics about spinal nerve subarachnoid spaces collect CSF to varying degrees (Koh et al. 2005).

Because lymph pressures are low (0-20 cm $H_2O$), lymphatic vessels are particularly sensitive to changes in hydrostatic and tissue pressures, which are altered with gravitational changes. It is known that lymphatics from different regions of the body adapt to their regional pressure and flow environments (Gashev et al. 2004). For example, 2 weeks of simulated microgravity in rats causes a potent inhibition of pressure/stretch stimulated pumping in all types of lymphatic vessels (Gashev et al. 2006). The largest pump flow inhibition was found in cervical lymphatics during simulated microgravity (Gashev et al. 2006). These lymphatics use cephalic to thoracic hydrostatic pressure gradient to generate lymph flow. Tracer studies suggest that CSF and extracranial lymph compartments are linked physiologically because tracers injected into the cranial cerebrospinal fluid later enter lymphatic vessels in the head and neck region (Koh et al. 2005). Animal studies (rat, dog, rabbit, and sheep) demonstrate that a large percentage (50%) of the CSF is cleared by the cervical and extracranial lymphatics (Boulton et al. 1999; Koh et al. 2005). In addition, silicon rubber tracer injected into the subarachnoid space of humans produced extensive infiltration into the lymphatic network adjacent to the extracranial surface of the cribriform plate and optic nerve (Johnston 2003; Koh et al. 2005). An increase in ICP resulted in greater levels of CSF tracer in the optic nerve and deep cervical lymph nodes (McComb et al. 1982). In fact, ligation of the cervical lymphatics result in edema of the brain and protein accumulation (Casley-Smith et al. 1976, 1978). However, it is unclear how impaired lymphatic function may contribute to vision impairment.

## 10. Glymphatics

The central nervous system does not contain traditional lymphatic vasculature. Recent data demonstrate that CSF moves within the periarterial space, providing a continuous pathway of interstitial fluid exchange (Iliff et al. 2012). Transport of water from the periarterial space into the brain parenchyma is facilitated by AQP4 water channels expressed in the membrane of astrocytes (Iliff et al. 2012, 2013) which "push" the brain parenchyma interstitial fluid into the perivenous space. From this perivenous space, the interstitial fluid can then empty into the cervical lymphatic system  (Johnston et al. 2004; Murtha et al. 2014). Moreover, this movement of periarterial CSF into and about the brain parenchyma was associated with movement of solutes to the perivenous sites (Iliff et al. 2012). Data suggest that lipids and lipoproteins greater than 1 kDa are localized to the perivascular space of the brain, and astrocytes release carrier proteins, thus the glymphatic pathway provides a route for lipid distribution. Rodent data suggest that the glymphatic pathways become enhanced during sleep, evidenced by the change in volume fraction of interstitial space of 14% during wake and 23% during sleep (Xie et al. 2013). Posture may play an additional role in the ability for the glymphatic system to clear waste during sleep. When rats are in the prone position, in which the head is most similar to the upright position and mimicking the awake state posture, glymphatic transport was a state of "retention", whereas, lateral and supine positions improved glymphatic transport (Lee et al. 2015). In addition,

norepinephrine may neuro-modulate the enhancement of the glymphatic system during sleep (Berridge and Waterhouse 2003).

It remains to be determined if and how a spaceflight-induced glymphatic dysfunction might play a role in the spaceflight-induced vision impairment. Denniston and Keane proposed that the paravascular system of the retina may be critical in retinal disease. Tracer studies indicate that similar "glymphatic" fluid pathways exist near the paravascular space around the central retinal artery and vein, but not in the lumen of the vessel itself. Sakamoto *et al.* proposed that the fluid communication zone occurs in the paravascular space around the branches of central retinal artery from the subarachnoid space to the optic nerve at the internal limiting membrane (Sakamoto et al. 2010). It remains unclear how this communication zone could be disrupted during spaceflight, however, as discussed above the TLPG and associated forces on this region may impact fluid communication from the retina to the optic nerve.

### F.  Structural Brain Changes

It is unknown if SANS is localized to the eye or if structural changes in the brain should be considered in describing the pathophysiology of SANS. Recent analysis of MRI data collected pre- and post-bed rest in 5 male and 3 female subjects suggests the brain may change (Roberts et al. 2015), but the physiological significance of these changes remains to be demonstrated. After 42 to 90 days of 6° head-down tilt bed rest there was a significant inferior-to-superior displacement of the brain by an average $0.36 \pm 15$ mm and the brain tended to rotate in left-right axis by $0.28 \pm 0.34$ degrees, as compared to values obtained pre bed rest. Ventricular volume changes from pre- to post-bed rest were seen in some subjects, but due to the large variability between individuals a change in ventricular volume for the group as a whole was not statistically significance. However, these authors suggested an association between brain rotation and percent change in ventricle volume. Moreover, there was a significant increase in both gray and white matter density at the brain vertex. While this study was limited to a small number of subjects and variable bedrest duration, these data suggest that head-down tilt bed rest may induce brain structure changes that could impact CSF flow and cerebral venous outflow pathways.

Recent retrospective analysis of 3 Tesla $T_2$-weighted brain MRIs collected before and after spaceflight suggests brain anatomical changes develop during long-duration, but not short-duration spaceflight (Roberts et al. 2017). Cine clips of matched pre- and post-flight images of 18 astronauts revealed narrowing of the central sulcus, enlargement of the ventricular system (lateral, third, and fourth ventricles), and a more frequent upward shift of the brain in long-duration (n=12) compared to short-duration (n=6) fliers. These authors hypothesize that the upward shift of the brain results in crowding of the vertex, obstruction of CSF and venous outflow, and results in elevation of ICP. Because only 3 astronauts in this cohort presented with optic disc edema, additional data are needed to understand if a relationship exists between SANS symptoms and brain structural changes. Indeed, further research is needed to explore this hypothesis and determine if these structural changes that appear in long-duration crewmembers represent pathological findings or are subclinical findings from exposure to prolonged weightlessness and resolve with time after return to a 1g environment.

It remains unknown if the structural changes and movement of the brain within the skull following bed rest or spaceflight result in alterations to venous outflow from the brain. MRI

venography evaluation may provide some information about venous compression and stenosis. Some potential compressive zones have also been proposed as possibly relevant in contributing to the venous congestion in microgravity (Wiener 2012).

### G. Sex

The incidence of SANS findings appears to be higher in male astronauts than in female astronauts, although the total number of female astronauts that have flown long-duration missions to the ISS remains low. During parabolic flight, Lawley, *et al.* measured ICP through the Ommaya reservoir of 5 male and 3 female subjects providing an opportunity to speculate on possible sex differences in the regulation of ICP. In this study, ICP during weightlessness was closer to the estimated 24 hour average ICP on Earth for the female subjects than it was for the male subjects. This suggests these female subjects experienced a greater translaminar pressure gradient in the posterior direction. Whether this difference between sexes occurs in astronauts during spaceflight and helps protect against the stimuli causing globe flattening is unknown and this hypothesis requires further investigation.

## VII.  CONCLUSIONS AND FORWARD WORK

Efforts by NASA to collect significant amounts of medical data on astronauts before, during, and after spaceflight have helped define the prevalence of ocular structural and functional changes that develop, while simultaneously investigating possible mechanisms, predictive risk profiles, and potential countermeasures. To date, 24 individual United States and partner agency astronauts have demonstrated one or more of the following signs: optic disc edema, globe flattening, choroidal folds, cotton wool spots, and/or change in refractive error. Based on the different number of individuals tested for each of these signs, 37 to 51% of long-duration crewmembers demonstrate one or more SANS findings. The inability to replicate SANS findings during bed rest, the most prevalent analog of spaceflight, has limited our ability to test various hypotheses on the ground. However, future planned bed rest studies include additional spaceflight-stressors such as elevated ambient $CO_2$, as well as possible relief of a headward fluid shift using artificial gravity during prolonged bed rest.

The initial leading hypothesis for the SANS risk was that long-duration spaceflight led to an increase in ICP that was transmitted to the posterior globe, leading to globe flattening, optic disc edema, and refractive error changes in some, but not all astronauts. However, no direct measure of ICP has been conducted during long-duration spaceflight to confirm or refute this hypothesis. Lawley *et al.* obtained direct measurements of ICP from a small number of subjects during short-duration weightlessness (~20 sec) in parabolic flight (Lawley et al. 2017), which provided some of the first evidence in humans to suggest that ICP may not be pathologically elevated. This study also provided insight into the role of exercise with and without a Valsalva maneuver, 24-hrs of bed rest, and the simple action of lifting the head during bed rest which may explain the lack of SANS signs during bed rest studies. Future work also needs to confirm if the few case studies reporting postflight lumbar puncture opening pressure truly represent elevated ICP by conducting preflight lumbar punctures for the appropriate within-subject comparison.

The data by Lawley (Lawley et al. 2017), in combination with the case study of the astronaut who completed a second spaceflight (Mader et al. 2013), and the number of SANS

signs that present asymmetrically between eyes (Mader et al. 2017) suggest that the underlying mechanism may involve the posterior globe, optic nerve, and/or tissue pressure and anatomy localized around the orbit. This hypothesis should be given greater investigative interest than it has previously received. As more optical coherence tomography images (which provide the most detailed and quantitative assessment of the posterior globe) are collected, we will develop a better understanding of the spatial and temporal time course of structural ocular changes.

Despite only partial understanding of the mechanisms or risk factors that contribute to the development of SANS, research into in-flight countermeasure development needs to be simultaneously investigated while we still have use of the ISS. Targeting the venous system that drains the head, the lymphatic system, and possible changes in cerebral spinal fluid all represent areas of research for possible countermeasure development or areas that may provide mechanistic insight that have not been fully investigated thus far. Studies are currently underway to investigate the use of devices that redistribute fluids distally, including Braslet thigh cuffs, a modified version of the Kaatsu system, an impedance threshold device, artificial gravity, and a lower body negative pressure device.

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## IX.    LIST OF ACRYONYMS

| | |
|---|---|
| AQP | Aquaporin |
| CCFP | Cochlear and Cerebral Fluid Pressure |
| ChT | Total choroid surface area |
| $CO_2$ | Carbon dioxide |
| CPG | Clinical practice guidelines |
| CSF | Cerebral spinal fluid |
| CVP | Central venous pressure |
| EJVP | External jugular venous pressure |
| EVA | Extra vehicular activity |
| HDT | Head-down tilt |
| ICP | Intracranial pressure |
| IIH | Idiopathic intracranial hypertension |
| IJVP | Internal jugular venous pressure |
| IOP | Intraocular pressure |
| LP | Lamina cribrosa |
| MRI | Magnetic resonance imaging |
| MRV | Magnetic resonance venogram |
| NFL | Nerve fiber layer |
| OA | Ophthalmic artery |
| OAE | Otoacoustic emission |
| OCT | Optical coherence tomography |
| ON | Optic nerve |
| ONH | Optic nerve head |
| ONS | Optic nerve sheath |
| ONSD | Optic nerve sheath diameter |
| POAG | Primary open angle Glaucoma |
| RNFL | Retinal nerve fiber layer |
| RPE | Retinal pigment epithelium |
| SMS | Space motion sickness |
| SSP | Sagittal sinus pressure |
| SVP | Spontaneous venous pulsations |
| VF | Visual field |

# X.    APPENDIX A

| ISS\Crew Member | Mission Duration | Refractive Change | Intraocular Pressure (mmHg) | Fundoscopic Exam Postflight | Disc Edema (Frisén) | OCT Postflight | Eye MRI Postflight / Globe Flattening | CSF Pressure Postflight (cmH2O) |
|---|---|---|---|---|---|---|---|---|
| CASE 1 | 6 months | Preflight: OD: -1.50 sph OS: -2.25-0.25x135 <br><br> Postflight: OD: -1.25 -0.25x005 OS: -2.50-0.25x160 | Preflight: 15 OU <br><br> Postflight: 10 OU | • Choroidal folds OD <br> • Cotton wool spot OD | Edema: No disc edema | • Choroidal folds still visible inferior to the OD disc (R+ >5yrs) | MRI not performed <br><br> Globe Flattening: Not assessed | Not measured |
| CASE 2 | 6 months | Preflight: OD: +0.75 OS:+0.75-0.25x165 <br><br> Postflight: OD: +2.00 sph OS: +2.00-0.50x140 | Preflight: 14 OU <br><br> Postflight: 14 OU | • Bilateral disc edema OD>OS <br> • Choroidal folds OD > OS <br> • Cotton wool spot OS | Edema: Grade 1 OD and OS | • NFL thickening c/w disc edema | Optic nerve sheath distension OD and OS <br><br> Globe Flattening: OD and OS | Elevated <br> • 22 at R+66 days; <br> • 26 at R+17 months; <br> • 22 at R+19 months) |
| CASE 3 | 6 months | Preflight: OD: -0.50 sph OS: -0.25 sph <br><br> Postflight: Plano Plano | Preflight: 10 OU <br><br> Postflight: 10 OU | • Bilateral disc edema OD>OS <br> • Small hemorrhage OD | Edema: Grade 3 OD Grade 1 OS | • Severe NFL thickening OD>OS c/w Disc edema | Optic nerve sheath distension OD <br><br> Globe Flattening: None observed | Elevated <br> • 21 at R+19 days |
| CASE 4 | 6 months | Preflight: OD: -0.75-0.50x100 OS: plano-0.50x090 <br><br> Postflight: OD: +0.75-0.50x105 OS: +0.75-0.75x090 | Preflight: 15/13 <br><br> Postflight: 11/10 | • Disc edema OD <br> • Choroidal folds OD | Edema: Grade 1 OD | • Mild NFL thickening OD>OS c/w disc edema <br> • Choroidal folds OD | Optic nerve sheath distension and tortuous optic nerves OD>OS <br><br> Globe Flattening: OD > OS | Elevated <br> • 28.5 at R+57 days |
| CASE 5 | 6 months | Preflight: OD: -5.75-1.25x010 OS: -5.00-1.50x180 <br><br> Postflight: OD: -5.00-1.50x015 OS: -4.75-1.75x170 | Preflight: 14/12 <br><br> Postflight: 14/12 | • Normal | Edema: No disc edema | • Subclinical disc edema <br> • Mild/moderate NFL thickening OD | Optic nerve sheath distension and tortuous optic nerves <br><br> Globe Flattening: OD and OS | Not measured |