Noninvasive Indicators of Intracranial Pressure Before, During, and After Long-Duration Spaceflight

Jessica V. Jasien[1], Steven S. Laurie[2], Stuart M.C. Lee[2], David S. Martin[2], David Kemp[3], Douglas J. Ebert[2], Robert Ploutz-Snyder[4], Karina Marshall-Goebel[2], Irina V. Alferova[5], Ashot Sargsyan[2], Richard W. Danielson[6], Alan Hargens[7], Scott A. Dulchavsky[8], Michael B. Stenger[9], Brandon R. Macias[9]

[1]JES Tech, Houston, TX, USA; [2]KBR, Houston, TX, USA; [3]University College London, London, UK; [4]University of Michigan, Ann Arbor, MI, USA; [5]Russian Federation State Research Center Institute of Biomedical problems, Russian Academy of Sciences, Moscow, Russia; [6]Baylor College of Medicine, Houston, TX, USA, [7]University of California, San Diego, CA, USA; [8]Henry Ford Hospital, Detroit, MI, USA; [9]NASA Johnson Space Center, Houston, TX, USA

Corresponding Author: Brandon R. Macias
Email: brandon.r.macias@nasa.gov
Address: NASA Cardiovascular and Vision Laboratory
2101 NASA Parkway Mail Code SK3
Houston, TX 77058

Running Head: Effect of spaceflight on ICP

Abstract (245/250 Words)

Weightlessness induces a cephalad shift of blood and cerebrospinal fluid that may increase intracranial pressure (ICP) during spaceflight, while lower body negative pressure (LBNP) may provide an opportunity to caudally redistribute fluids and lower ICP. To investigate the effects of spaceflight and LBNP on noninvasive indicators of ICP (nICP), we studied thirteen crewmembers before and after spaceflight in seated, supine, and 15° head-down tilt postures, and at ~45 and ~150 days of spaceflight with and without 25 mmHg LBNP. We used 4 techniques to quantify nICP: cerebral and cochlear fluid pressure (CCFP), otoacoustic emissions (OAE), ultrasound measures of optic nerve sheath diameter (ONSD), and ultrasound-based internal jugular vein pressure (IJVp). On flight day 45, two nICP measures were lower than preflight supine posture (CCFP: mean difference -98.5 -nl [CI: -190.8 to -6.1 -nl], p = 0.037]; OAE: -19.7 degrees [CI: -10.4 to -29.1 degrees], $p < 0.001$), but not significantly different from preflight seated measures. Conversely, ONSD was not different than any preflight posture, whereas IJVp was significantly greater than preflight seated measures (14.3 mmHg [CI: 10.1 to 18.5mmHg], $p < 0.001$), but not significantly different than preflight supine measures. During spaceflight, acute LBNP application did not cause a significant change in nICP indicators. These data suggest that during spaceflight nICP is not elevated above values observed in the seated posture on Earth. Invasive measures would be needed to provide absolute ICP values and more precise indications of ICP change during various phases of spaceflight.

New & Noteworthy: The current study provides new evidence that intracranial pressure (ICP), as assessed with noninvasive measures, may not be elevated during long-duration spaceflight. Additionally, the acute use of lower body negative pressure did not significantly reduce indicators of ICP during weightlessness.

Introduction

When optic disc edema, globe flattening, choroidal folds, and hyperopic shifts were first reported in astronauts following long-duration spaceflight, some hypothesized that prolonged exposure to weightlessness caused a pathological elevation in intracranial pressure (ICP) leading to ocular findings similar to those in patients with idiopathic intracranial hypertension (IIH) (1, 2). Therefore, these ocular changes were originally named the visual impairment and intracranial pressure (VIIP) syndrome, despite the fact that the sentinel report highlighted multiple hypotheses not related to ICP as the cause of the ocular findings (1). As reports were published of additional structural changes to the eye (3–7) and brain (8–13) during spaceflight and brief periods of weightlessness in parabolic flight (14), the National Aeronautics and Space Administration (NASA) renamed the risk spaceflight associated neuro-ocular syndrome (SANS) to better allow for a broad range of etiological possibilities for the cause of the neuro-ocular findings in crewmembers.

On Earth, moving from seated to supine posture increases ICP by ~10-15 mmHg (~14-20 cmH_2O), and during 15° head-down tilt (HDT) ICP increases by an additional ~5 mmHg (~7 cmH_2O) (15–17). Direct measures of ICP obtained in the supine posture during ~20 seconds of weightlessness induced by parabolic flight demonstrated that ICP was not elevated, but rather slightly less than the ICP measured in the supine posture during 1g (13 mmHg while weightless vs 15 mmHg in 1g), although ICP was higher than that measured while seated in 1g (4.1 mmHg) (14). While ICP has never been directly measured in astronauts during spaceflight, postflight lumbar puncture opening pressure (LPOP) of cerebrospinal fluid pressure (CSFP) has been measured in a subset of long duration astronauts presenting with Frisèn grade optic disc edema, with CSFPs ranging from 12 to 21 mmHg (16 to 29 cm H_2O) (1, 7, 18). Because some of these pressures are considered to be higher than normal (19), it was hypothesized that spaceflight may cause changes in CSF homeostasis that result in an augmented response of

ICP to posture changes and therefore an increased ICP after flight when crewmembers are placed in the lateral decubitus posture for the lumbar puncture procedure (1). Thus, there remains a need to measure ICP during and following long-duration spaceflight in astronauts who present with and without optic disc edema to determine what role ICP may have in the observed ocular and brain changes of astronauts.

Techniques for assessing nICP include cerebral and cochlear fluid pressure (CCFP) (1, 5, 7, 14, 20, 21), otoacoustic emissions (OAE) (22, 23), and the use of ultrasonography to measure optic nerve sheath diameter (ONSD) (24, 25). Where CCFP values correlate with tympanic membrane displacement (TMD) (1, 5, 7, 14, 20), OAE measures correlate with the tension of the oval window and the middle ear (22, 23), and ONSD measures the engorgement of the optic nerve sheath due to accumulation of cerebrospinal fluid (CSF) near the optic nerve head (ONH) (24, 25). Noninvasive indicators of internal jugular vein pressure (IJVp) (18) also may reflect ICP, because pressure in the dural venous sinuses has a direct effect on ICP (26).

The aim of this study was to use multiple noninvasive methods to assess ICP before, during and after long-duration spaceflight. A secondary aim was to determine if use of lower body negative pressure (LBNP), a technique that sequesters blood volume in the lower body, could reduce ICP during spaceflight. We hypothesized that nICP indicator measurements during spaceflight would be significantly greater compared to the upright posture on Earth. Additionally, we hypothesized that the use of LBNP would decrease nICP measures. To accomplish these aims, we assessed crewmembers before and after spaceflight in multiple postures on Earth, and during spaceflight with and without use of LBNP. Using these data, we sought to determine: (1) how noninvasive indicators of ICP during spaceflight compare to noninvasive measures of ICP in various postures on Earth, (2) the effect of LBNP on nICP indicators during spaceflight, and (3) if the change in nICP indicators due to posture changes is augmented after spaceflight.

Methods

Study Design

This NASA funded study known as “Fluid Shifts” included co-investigators from multiple institutions and international partners, and other data from this cohort have previously been reported (27–29). Thirteen crewmembers (2 females, 11 males; mean ± standard deviation [SD]: 46±6.6 years old; 81.5±9.5 kg) from multiple space agencies provided written informed consent to participate in this study and participated in a (mean ± SD) 215 ± 72-day mission to the International Space Station (ISS). The study protocol was approved by the NASA Johnson Space Center Institutional Review Board (protocol #0701), the Human Research Multilateral Review Board, and internal review boards from the respective international space agencies.

A schematic of the testing timeline is provided in Figure 1 with the mean and the SD of data collection days. Preflight (Pre) and postflight (return [R]+10 days, R+30 and R+180) testing occurred in the seated, supine, and 15° HDT postures. Before data collection, crewmembers were stabilized in each posture for 5 minutes and data were collected in the same order during each posture. The inflight measures on the ISS occurred around flight day 45 (FD45) and 150 (FD150). During flight, data were collected at baseline without LBNP, and approximately 1 week later with 25 mmHg LBNP (Russian Chibis-M LBNP) for ~60 minutes; testing during LBNP at each FD45 and FD150 required two 60-minute session, typically separated by 1-2 days. The postflight R+10 data collection session included only 8 of the 13 crewmembers because the testing required immediate postflight travel to NASA Johnson Space Center after return to Earth.

Noninvasive Indicators of ICP

The CCFP analyzer (MMS-11 Tympanic Displacement Analyzer, Marchbanks Measurement Systems, Ltd., Lymington, Hampshire, United Kingdom) elicits a tone that causes stapedius muscle contraction and TMD. The direction and magnitude of the TMD movement correlates with direct ICP magnitude (20) due to the direct communication of the perilymph and CSF through the cochlear aqueduct (21, 30–33) which results in a pneumatic volume change of the ear canal, measured in nanoliters. The units were inverted to more intuitively relate to changes in pressure (scale reversed from nl to -nl). During the preflight session, a middle ear analyzer (GSI TympStar Pro) was used to determine the acoustic reflex threshold and to set the stimulus intensity presented by the CCFP analyzer, with a maximum of 110 dB hearing level. The same intensity of CCFP analyzer stimulus intensity was used for a given subject at all data collection sessions, and the mean of 20 stimuli from each session was used for statistical analysis. During preflight and postflight testing, CCFP measures were obtained ~15 minutes into each posture condition, while this measure was collected after ~5 minutes of use of LBNP application during spaceflight, as previously described (20).

Transient evoked OAE methods, which apply broadband click stimuli, were employed as noninvasive indices of ICP change and were previously described in detail (34). The association between OAE and direct ICP measures relies on the pressure communication between perilymph and cerebral spinal fluid; altered stiffness of structures within the middle ear results in a frequency specific phase in the OAE response signal relative to a reference condition’s OAE response (22, 23). Each subject’s conglomerate OAE response from all conditions was used as the arbitrary zero value for phase, against which each individual condition was compared and reported as a raw phase value. Phases are read from the plotted data as the difference between a reference value (such as seated) and the condition of interest. During preflight and postflight testing transient-evoked OAE recordings were obtained ~5 minutes after assuming each posture. During spaceflight OAE measures were obtained ~1 week prior to the LBNP session and ~30-45 minutes after starting LBNP. OAE responses were recorded from 600 Hz to 6 kHz along with the ear canal acoustic stimulus response as a quality control, using the Otoport Advance OAE analyzer (Otodynamics, Hatfield, UK). All recordings were obtained from the right ear. One recording was made for each condition during preflight and postflight testing. Inflight recordings were taken in duplicate, with a complete removal and reseating of the ear canal probe to maximize the likelihood for optimal fit; all data were used unless they did not meet quality criteria as described below. OAEs were analyzed for each crewmember in three individualized frequency bands in the 0.7-1.7 kHz range (22, 35), which remained fixed for all the analyses of all conditions for that crewmember. Recordings (all bands) were considered unusable if 50% or more of the acoustic stimulus phase or intensity data points across the entire recorded frequency range were more than two standard deviations from the mean of each subject's conglomerate acoustic stimulus (all conditions); 13 recordings were excluded out of 275. Individual band data were excluded if the signal-to-noise ratio was less than 6 dB (43 bands were excluded of 825 total).

Ocular ultrasound was obtained in the right eye ~20 minutes after assuming each posture during preflight and postflight testing. During spaceflight with LBNP, ONSD measures were obtained by crewmembers ~5-10 minutes after applying LBNP. However, ONSD measures did not occur on the same day as the CCFP and OAE measures in LBNP. At each data collection session, 3 images were obtained with the GE Vivid Q ultrasound device (GE Healthcare, USA) using a 12 MHz linear probe (36). Ultrasound images of the ONSD were obtained by crewmembers on ISS during spaceflight with real-time guidance. ONSD was manually measured by two independent sonographers using GE EchoPAC software (GE Healthcare, United States) 3 mm posterior to the ONH. If the measurements of ONSD from an ultrasonographic image differed by more than 10% (20% for seated posture), an additional sonographer analyzed the image. If these quality criteria could not be achieved due to poor image quality, the measurement was not included in the data set (1/632 of measures were excluded).

Noninvasive indicators of IJVp, which have been correlated with direct measures of ICP in previous experiments (26), were obtained ~35 minutes after assuming each posture during preflight and postflight testing, as previously described (18). Briefly, the VeinPress device was zeroed prior to each measurement, the subject was instructed to inhale and exhale to functional residual capacity and hold their breath briefly. The IJV was compressed until both walls of the vessel touched and the subject was instructed to breathe normally. IJVp measures were not obtained during LBNP because this measure was added to the spaceflight arm late in the implementation of the study and the appropriate approvals were not obtained by the time the study started. The VeinPress compression sonography device (Meridian AG, Switzerland) uses a translucent fluid-filled bladder attached to a manometer, secured to a 12-5 MHz linear array ultrasonographic probe (GE Healthcare, USA) (18, 28). Noninvasive indicators of IJVp are determined by observing the pressure required to fully compress the IJV (lumen walls touching). Two to three measurements were obtained at each time point and two independent sonographers reviewed videos and still images to determine the pressure at wall collapse and tissue contact, as previously described (18, 28). A subset of the IJVp data included herein have been previously published by our group (28); however, here we report the complete dataset with three additional subjects.

During preflight and postflight testing on Earth the order of data collection for the nICP indicators was OAE, CCFP, ONSD, and IJVp. However, during spaceflight due to the crewmembers being at steady state with no change in posture and due to scheduling constraints related to conducting spaceflight research, the order of measures was not always the same. For most of the sessions, ONSD and IJVp measurements preceded the CCFP and OAE measurements.

During use of LBNP, ONSD was measured on the first LNBP day along with other ultrasound measures, and on the second LBNP day CCFP was first and OAE was last.

Statistical Analyses

Statistical analyses were performed using Stata software (StateCorp. LLC, 2019. Stata Statistical Software: Release 16. College Station, TX), with an emphasis on characterizing the observed effects with modeled means and 95% confidence intervals. Statistically significant differences were determined against a 2-tailed null hypothesis of no-differences with α=0.05. All model assumptions were evaluated prior to reporting effects, resulting in the elimination of a few observations per outcome that produced standardized residuals exceeding ± 2 units, based on the measure used, in order to meet model assumptions. Our experimental design is longitudinal in nature, with astronauts providing data from each of three postures pre- and postflight (seated, supine, HDT), and two in-flight conditions observed at two time periods (spaceflight, spaceflight+LBNP). In addition, some of the outcomes were measured in replicate within each time point to increase precision as described above (ex. IJVp was measured in triplicate each time).

We submitted each of our continuously scaled outcomes to separate statistical mixed-models with a-priori fixed effects parameters. We first compared FD45 spaceflight to all posture combinations preflight. Next, we analyzed the inflight data (FD45 and FD150) collected with and without LBNP for our evaluation of the effects of LBNP in microgravity. Finally, we evaluated posture changes before and after spaceflight to determine effects of day or posture, as well omnibus interaction effects. All models included random Y-intercept to accommodate the within-subjects experimental design. All data are presented as the marginal means ± 95% confidence intervals (CI) unless otherwise noted.

Results

Effect of Posture and Spaceflight on nICP

Posture changes from seated to supine and seated to 15˚HDT resulted in a statistically significant mean increase in nICP indicators for all 4 measurement methods (Table 1, shown in Figures 2 and 4, although statistical analyses are not reflected in these figures).

On FD45 during spaceflight the CCFP-acquired TMD estimate of nICP was lower than the TMD measured preflight in the supine posture (mean difference: -98.5 -nl [CI: -190.8 to -6.1 -nl], *p*=0.037) and 15° HDT posture (mean difference: -182.9 -nl [CI: -275.2 to -90.6 -nl], *p*<0.001), but not significantly different from the preflight seated posture (mean difference: 7.1 -nl [CI: -85.2 to 99.4 -nl], *p*=0.879). Similarly, the OAE phase on FD45 was also significantly lower than the preflight supine posture (mean difference: -19.7 degrees [CI: -10.4 to -29.1 degrees], *p*<0.001) and 15° HDT posture (mean difference: -41.9 degrees [CI: -32.2 to -51.6 degrees], *p*<0.001), but not statistically different than the preflight seated posture (mean difference: 2.4 degrees [CI: -7.3 to 12.1 degrees], *p*=0.627). At FD45 the mean change in ONSD was not significantly different compared to any preflight posture (mean differences - seated: -0.026 cm [CI: -0.056 to 0.005 cm], *p*=0.099; supine: (0.012 cm [CI: -0.017 to 0.042 cm], *p*=0.408; or 15° HDT (0.023 cm [CI: -0.006 to 0.052 cm], *p*=0.117). During spaceflight on FD45 the change in IJVp was not statistically different than the preflight supine posture (mean difference: -2.6 mmHg [CI: -6.6 to 1.5 mmHg], *p*=0.21), but was greater than the preflight seated mean measures (mean difference: 14.3 mmHg [CI: 10.1 to 18.5 mmHg] *p*<0.001) and less than the 15° HDT mean measures (-4.1 mmHg [CI: -0.1 to -8.2 mmHg] *p*=0.047). During spaceflight the mean nICP indicator measures between FD45 and FD150 were not significantly different from each other (CCFP: 53.0 -nl [CI: -39.6 to 145.6 -nl] *p*=0.256; OAE: 6.96 degrees [CI: -0.8 to 14.7 degrees] *p*=0.078; ONSD: (0.006 cm [CI: -0.023 to 0.035 cm] *p*=0.688; IJVp: -2.2 mmHg [CI: -6.4 to 2.0 mmHg] *p*=0.296).

Effect of LBNP during Spaceflight on nICP

Of the 3 techniques that were evaluated with LBNP during spaceflight, only OAE showed a significant nICP indicator change (Figure 3). All changes in nICP indicator measures were compared to the baseline values obtained on FD45 (FD45 Spaceflight). There was no significant difference in CCFP-acquired TMD between FD45 with and without LBNP (mean difference: -16.73 -nl [CI: -66.53 to 33.07 -nl] *p*=0.496) and FD150 with LBNP (mean difference: -29.85 -nl [CI: -81.55 to 21.85 -nl] *p*=0.246). Similarly, there was no change in ONSD with use of LBNP on FD45 (mean difference: -0.002 cm [CI: -0.032 to 0.028 cm] *p*=0.895) or FD150 with LBNP (mean difference: 0.004 cm [CI: -0.026 to 0.034 cm] *p*=0.791) or the OAE phase on FD45 with LBNP (mean difference: -1.8 degrees [CI: -8.3 to 4.6 degrees] *p*=0.577). On FD150 with LBNP, the change in the OAE phase was statistically significant, indicating that LBNP induced a higher middle ear tension (mean difference: 9.0 degrees [CI: 2.1 to 15.8 degrees] *p*=0.01).

Effect of Spaceflight on the Response of nICP Indicators during Postflight Posture Changes

To determine if spaceflight caused an augmented response of the nICP indicators during posture changes, we investigated if the nICP indicator responses to posture changes postflight were significantly different than preflight testing time points. The omnibus interaction between posture and time was only significant for OAE (Table 1). Similar to the preflight posture changes, preflight and postflight tests demonstrated a main effect for posture, with progressive increases in noninvasive indicators of ICP with postural changes from the seated to supine and HDT postures (Table 1, Figure 4).

Of the 13 crewmembers studied, Space Medicine Operations determined that one presented with Frisèn grade 1 optic disc edema during spaceflight and had a postflight CSFP of 16.2 mmHg (22 cm H_2O) 7 days after returning to Earth, which is below the threshold of direct ICP measurements for intracranial hypertension (1, 7, 37). No additional direct measures of ICP are available for other crewmembers in the current study.

Discussion

The majority of nICP indicators used in the present study demonstrate that spaceflight values are not significantly different from the seated posture observed before spaceflight. These are noninvasive estimates of ICP change and each technique utilizes a different physiological mechanism as an indicator of ICP. Therefore, because each technique relies on a different physiological relationship to ICP some differences among the measures are expected and definitive conclusions regarding the true ICP levels during long duration spaceflight will require invasive gold standard measures of ICP. Unfortunately, due to the invasive nature of directly measuring CSF pressure via lumbar puncture, inflight measures of ICP on the ISS have not been performed. However, the nICP indicator data presented here provide important new information about the relative pattern of ICP change during long duration spaceflight as compared to various posture conditions on Earth.

On Earth, direct measures of ICP document a posture-induced increase in ICP from the upright to the supine body position, highlighting the diurnal fluctuations in ICP that occur during a 24-hour period, with about two-thirds of the day spent in the upright posture (14, 16, 17). The normal reference values of directly measured ICP in the upright and supine positions are approximately 1 mmHg (-5.9 to 8.3 mmHg (1.3 cmH_20 (-8.7 to 11.2))) and 8.6 mmHg (0.9 to 16.3 mmHg (11.7 cmH_20 (1.2 to 22.2 cmH_20))), respectively (38). In addition, ICP measured in the 15˚HDT posture is ~26 ± 4 mmHg (39). In a majority of the four different noninvasive ICP approaches, we observed the expected posture-induced increase (18, 20, 22–26) before and after flight. While three of these nICP indicators demonstrate a similar and expected pattern of posture-induced change, the ONSD measure in the present study was not sufficiently sensitive to detect this known change in ICP. Therefore, we focus our interpretation of the spaceflight-induced change in nICP indicators on TMD, OAE and IJVp outcome measures.

The TMD and OAE nICP indicators demonstrate that values during long duration spaceflight are similar to those observed in the seated posture. Invasive ICP measures during acute weightlessness in parabolic flight demonstrated a significant decrease in ICP when transitioning from 1g to 0g in the supine posture by 3.8 ± 2.9 mmHg (mean 15 ± 2 mmHg in 1g and 13 ± 2.6 mmHg during 0g), supporting the idea that ICP during spaceflight may be less than when in the supine posture on Earth but remains greater than the value in the seated posture. This suggests that there may be ICP-lowering fluid volume adaptations during prolonged spaceflight that do not develop during 20 seconds of weightlessness. Indeed, IJV area during acute weightlessness in parabolic flight was twice as large as IJV area measured supine (14), whereas IJV area measured after ~45 days of spaceflight was similar to preflight values in the supine posture (28). Our FD45 measures of IJVp were not significantly different from the supine posture, but some limitations in this measurement approach may address this finding. During spaceflight the TMD and OAE nICP indicator values were significantly less than those in the supine posture and not different from the seated upright posture, whereas weightlessness IJVp measures where not significantly different from preflight supine values. However, these three ICP indicators during spaceflight were less than measures during the 15˚HDT posture with invasive ICP documented to be ~26 ± 4 mmHg (39). Therefore, we are cautious to draw a definitive conclusion in regard to how similar spaceflight IJVp values are relative to the seated or supine postures on Earth. Previous reports document that ICP in the supine posture is approximately ~9 mmHg (38), therefore the present data further suggest that ICP during spaceflight would be below this value.

All of the nICP indicators used in this study track ICP changes indirectly and do not produce an absolute ICP value. Further, each ICP indicator technique relies on a different physiological mechanism to detect change, and may explain why the spaceflight to supine IJVp trends were different than those detected with TMD or OAE methods. During seated posture the IJVs often are collapsed as the majority of blood from the head drains through the vertebral veins. There may be a difference in the relationship between ICP within the skull, IJVp measured outside the skull, and the resulting changes in central venous pressure within the thorax. Indeed, during parabolic flight supine subjects entry into weightlessness led to a drop in central venous pressure, concomitant with a drop in ICP, yet IJV area increased by ~100% (0.5 cm^2 to 1.0 cm^2). It is also possible that the absolute value of IJVp if measured invasively would be lower than that measured with the present IJVp technique. This difference may occur because the pressure value that we record is at full collapse of the vessel which may over estimate an invasively measured pressure. Further there may be some IJVp device gravity dependencies that have yet to be identified, however these were not evident in our use of the device. The IJVp spaceflight values are similar to those in the supine posture on Earth, but for the reasons outlined above some caution is warranted in concluding that these IJVp data suggest that ICP during spaceflight is greater than the seated body posture on Earth.

The ICP indicators measured during spaceflight in the present study were mostly similar to the seated posture on Earth. The finding that spaceflight IJVP values are similar to supine posture, and OAE and TMD are similar to seated may help explain why ONH edema tends to be mild or subclinical in most SANS cases. Further work is needed to understand if the lack of diurnal change in ICP contributes to the development of neuro-ocular changes observed in some astronauts during long-duration spaceflight. Since our current conclusions are based on cohort mean values, it is also still possible that ICP is chronically and mildly elevated in a subset of astronauts, which could lead to SANS.

We also designed this study to investigate if LBNP application during spaceflight could be used to lower ICP. LBNP is a technique used to sequester fluid in the lower limbs and has historically been used as a technique to evaluate cardiovascular physiology and function through a reduction in venous blood volume returning to the heart (40, 41). Here, we implemented the use of a moderate level of LBNP (25 mmHg) to minimize untoward cardiovascular stress and thus reduce the possibility of crewmembers developing symptoms of presyncope. When healthy subjects on Earth were exposed to 20-30 mmHg of LBNP while in the supine posture, which based on IJV area elicits a similar venous headward fluid shift as occurs during spaceflight (28), LBNP did not impair cardiac output or cerebral perfusion pressure (34, 39). During spaceflight, we did not observe a significant reduction in nICP indicators during use of 25 mmHg LBNP. One likely explanation for this finding is that the baseline ICP surrogate values were not significantly elevated. Direct invasive ICP measures in healthy subjects during moderate levels of LBNP (20 to 30 mmHg) in the supine posture reduced ICP by only ~3 to 4 mmHg (39). Thus, if a similar magnitude decrease in ICP occurred in crewmembers during spaceflight studied in the present study our noninvasive approaches may not have had the sensitivity to detect a change induced by LBNP (42, 43). When subjects were exposed to 15° HDT on Earth, ICP was elevated to ~26 ± 4 mmHg and use of the same moderate level of LBNP (20-30 mmHg) reduced ICP by 6 to 8 mmHg (39). These data highlight that use of LBNP may have a greater magnitude effect at higher baseline ICP levels and less of an effect at lower ICP values, which is consistent with the nonlinear intracranial pressure-volume curve (42). Therefore, based on the intracranial compliance, the effectiveness of LBNP at lowering ICP is dependent on ICP magnitude. Larger reductions in ICP would likely be possible when LBNP reduces the headward fluid shift in individuals operating at the higher end of their intracranial compliance curve. The fact that LBNP did not reduce ICP in these experiments is therefore further evidence that ICP is not substantially elevated during spaceflight.

The potential role for LBNP as a SANS countermeasure may not rely solely on ICP outcomes. Previously, we reported in the same subjects studied here that 25 mmHg LBNP causes a reduction of IJV area and pressure and improvements in IJV flow in some crewmembers during spaceflight (34). This suggests that the spaceflight-induced headward fluid shift in the cerebral venous compartment can be altered by LBNP, despite the lack of a direct effect on nICP indicators as reported here. However, invasive measures of ICP would have greater sensitivity and higher fidelity to definitively document the effects of mechanical countermeasures on ICP. It is important to note that LBNP reduces intraocular pressure during spaceflight which suggests an effect on ocular venous hemodynamics (29). This highlights the reality that ICP should not be the only outcome measure used to determine the effectiveness of possible SANS fluid shift countermeasures(44), especially given that ICP has not been proven to be the sole cause of SANS.

While these nICP indicators did not demonstrate significant effects of 25 mmHg LBNP on ICP during spaceflight, it is possible that the effect of LBNP on the cerebral vasculature could reduce capillary pressure at the optic nerve head, and thereby reduce the development of optic disc edema, independent of changes to ICP. Mean arterial pressure at the level of the eye is elevated during weightlessness relative to the upright posture on Earth because of the lack of a hydrostatic column (20, 45). Engorgement of the IJV is evident during weightlessness (14, 28) and reduced with LBNP (28). Thus, if venule and arterial pressure are elevated this would result in increased capillary pressures. Similar to the cerebral microcirculation, the retinal microvasculature contains blood-brain barrier proteins and tight junctions that should effectively prevent changes in arterial and venous pressure from causing increased capillary filtration and accumulation of extra-vascular fluid. Indeed, despite arterial and venous pressures affecting the entire retinal vasculature equally, we do not observe edema throughout the entire retina (3, 47).

Instead, we have previously hypothesized (3) that the lack of blood-brain barrier markers in the prelaminar region of the optic nerve head (47) may make this region specifically susceptible to increases in capillary filtration secondary to elevated arterial and venous pressures in this region. Therefore, if reducing venous pressure at the level of the eye, independent of effects on ICP, causes a reduction in capillary filtration that contributes to optic disc edema, then LBNP represents a potential approach to mitigate SANS. This notion is independent of any potential changes to TLPD, which are possible with LBNP use. LBNP during spaceflight reduces IOP by ~1.4 mmHg in the same subjects studied here (29) and if ICP during spaceflight is similar to the seated posture on Earth and unchanged by LBNP, then TLPD could in theory be reduced by 1-2 mmHg. Given that daily posture changes on Earth change TLPD by ~10 mmHg it seems unlikely that reducing TLPD by ~1-2 mmHg during LBNP use would negatively affect the optic nerve head, however this potentially deleterious effect of LBNP should be considered during interpretation and application of data collected during LBNP experiments.

Direct measures of ICP in six astronauts have been collected in those presenting with Frisèn grade 1 edema or greater after return from long-duration spaceflight missions (Table 2) (1, 7, 37). Interestingly, the range of the postflight ICP values reported in astronauts with optic disc edema were similar to the ICP values reported in healthy individuals before parabolic flight (14). Despite this, some have considered these values in astronauts postflight to be at the higher end of normal, and two exceeded the 25 cmH_2O (18.4 mmHg) threshold of IIH (1, 7, 37), although there are data that support raising the ICP threshold for IIH diagnosis to 30 cmH_2O (46). We and others have hypothesized that spaceflight may have changed the shape of the intracranial compliance curve. Even if the mean ICP is unchanged, there may be a higher ICP pulse amplitude. However, these data have not been reported in astronauts and these nICP indicator data only provide estimates of the mean change in ICP and do not provide insight into the ICP pulse amplitude. Invasive ICP measures of pulse amplitude would be highly beneficial in directly addressing changes in craniospinal compliance.

Since each of the nICP indicator methods have limitations, we chose to use multiple approaches to demonstrate consistent findings across techniques and therefore increase confidence in the interpretation of the findings of the overall cohort. The crewmember with Frisèn grade optic disc edema did not demonstrate consistently different nICP indicator findings relative to other participants in this cohort. While this subject appeared to demonstrate a larger shift in OAE phase during spaceflight, this finding was not replicated by the other nICP indicator approaches. Recent reports of optic disc edema in crewmembers assessed using optical coherence tomography suggest that early signs of optic disc edema are present in most crewmembers (3, 5). This indicates that there is some common cause that we have not detected in these experiments, and due to the inconsistency in the nICP indicators in this single SANS case in our cohort, we cannot conclude that ICP was a primary contributor to SANS in this subject. The nICP indicators of the present study provide insight into ICP at a single point in time and represent a time averaged value over the course of the measurement. We acknowledge that these nICP indicator techniques do not provide an absolute ICP value in units of pressure, and as an indirect measure may not follow the same nonlinear intracranial pressure-volume curve. Finally, we acknowledge that the inflight measures of nICP indicators with and without LBNP were not collected on the same study day. Due to crewmember scheduling constraints, coordination of moving equipment between the US and Russian modules on the ISS, and the total time needed to conduct all experiments, the measures needed to be obtained on separate study days.

In conclusion, these data demonstrate that the nICP indicators during spaceflight are overall similar to measures obtained in the seated posture on Earth, with three of the four measures demonstrating values not different than those obtained in the seated posture. LBNP did not lower nICP indicators during spaceflight, possibly because ICP was not substantially elevated. Future investigations of invasive gold standard measures of ICP would provide absolute ICP values and more specific pressure change values, but the results presented here further our understanding of ICP during and after long-duration spaceflight.

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Disclosures

No conflicts of interest, financial or otherwise, are declared by the authors.

Author Contributions

S.S.L., S.M.L., D.S.M., A.S., D.J.E., A.H., M.B.S., and B.R.M. conceived and designed the experiments. A.H., M.B.S., B.R.M., and S.S.L. performed the experiments. J.V.J., D.J.E., D.K., R.W.D., R.P.S., S.S.L., B.R.M. analyzed data from the experiments. J.V.J., D.J.E. S.M.L., D.K. R.P.S., K.M.G., A.H., M.B.S., B.R.M., and S.S.L prepared and drafted the manuscript. All authors contributed to the intellectual input into analyzing and writing the manuscript.

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Figure and Table Legend

Figure 1. Testing timeline of each data collection session and posture tested. All four noninvasive intracranial pressure indicator techniques were used for each testing session, except IJVp was not used during spaceflight with LBNP. Preflight (pre), flight day 45 (FD45), flight day 150 (FD150), postflight day 10 (R+10), postflight day 30 (R+30), postflight day 180 (R+180).

Figure 2. Noninvasive indicators of intracranial pressure including (A) cerebral and cochlear fluid pressure-derived tympanic membrane displacement (TMD; -nl), (B) otoacoustic emission-derived phase (OAE; degrees), (C) optic nerve sheath diameter (ONSD; cm), and (D) internal jugular vein pressure (IJVp; mmHg) from all subjects preflight in various postures and inflight on flight days 45 (FD45) and 150 (FD150). Black round symbol connected by black line is the crewmember identified with Frisen grade 1 optic disc edema. In multiple instances the individual data point appears similar to the mean. Dark horizontal bar is the mean with 95% confidence interval, and gray data points show individual subject data. * $p < 0.05$ versus FD45 Spaceflight.

Figure 3. Spaceflight (FD45 and FD150) and spaceflight with LBNP (FD45 LBNP and FD150 LBNP) nICP indicator measures from all subjects. The use of LBNP during spaceflight did not have an effect on nICP indicators. Measures include (A) cerebral and cochlear fluid pressure-derived tympanic membrane displacement (TMD; -nl), (B) otoacoustic emission-derived phase (OAE; degrees), and (C) optic nerve sheath diameter (ONSD; cm). Black round symbol connected by black line is the crewmember identified with Frisen grade 1 optic disc edema. In multiple instances the individual data point appears similar to the mean. Dark horizontal bar is the mean with 95% confidence interval. Dark horizontal bar is the mean with 95% confidence interval, and gray data points show individual subject data. * $p < 0.05$ versus FD45 Spaceflight. Note that nICP indicator measures with and without LBNP occurred approximately one week apart.

Figure 4. Noninvasive indicators of intracranial pressure including (A) cerebral and cochlear fluid pressure-derived tympanic membrane displacement (TMD; -nl), (B) otoacoustic emission phase (OAE; degrees), (C) optic nerve sheath diameter (ONSD; cm), and (D) internal jugular vein pressure (IJVp; mmHg) from all subjects preflight and postflight (return to Earth [R+] R+10, R+30, R+180 days) in various postures. The omnibus interaction between posture and time was not significant for any nICP outcome. Black round symbol connected by black line is the

crewmember identified with Frisen grade 1 optic disc edema. In multiple instances the individual data point appears similar to the mean. Dark horizontal bar is the mean with 95% confidence interval, and gray data points show individual subject data. Note that in some cases the symbol representing the individual with Frisèn grade edema appears similar to the horizontal bar at the mean. The dotted vertical line separates preflight from postflight.

Table 1. Mean mixed-effects coefficients, *p*-values, and 95% confidence intervals of simple effects of day, posture, and the omnibus interactions.

Table 2. Postflight lumbar puncture opening pressure of CSFP measured in 1 crewmember from the current publication and measures reported in previous publications. Each row represents CSFP measures from an individual crewmember. The normal range of CSFP is 14.7-18.4 mmHg (20-25 cmH_20).

Figure 1

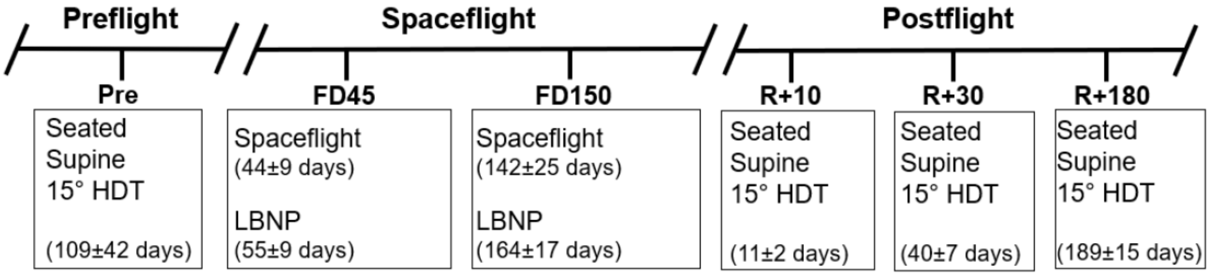
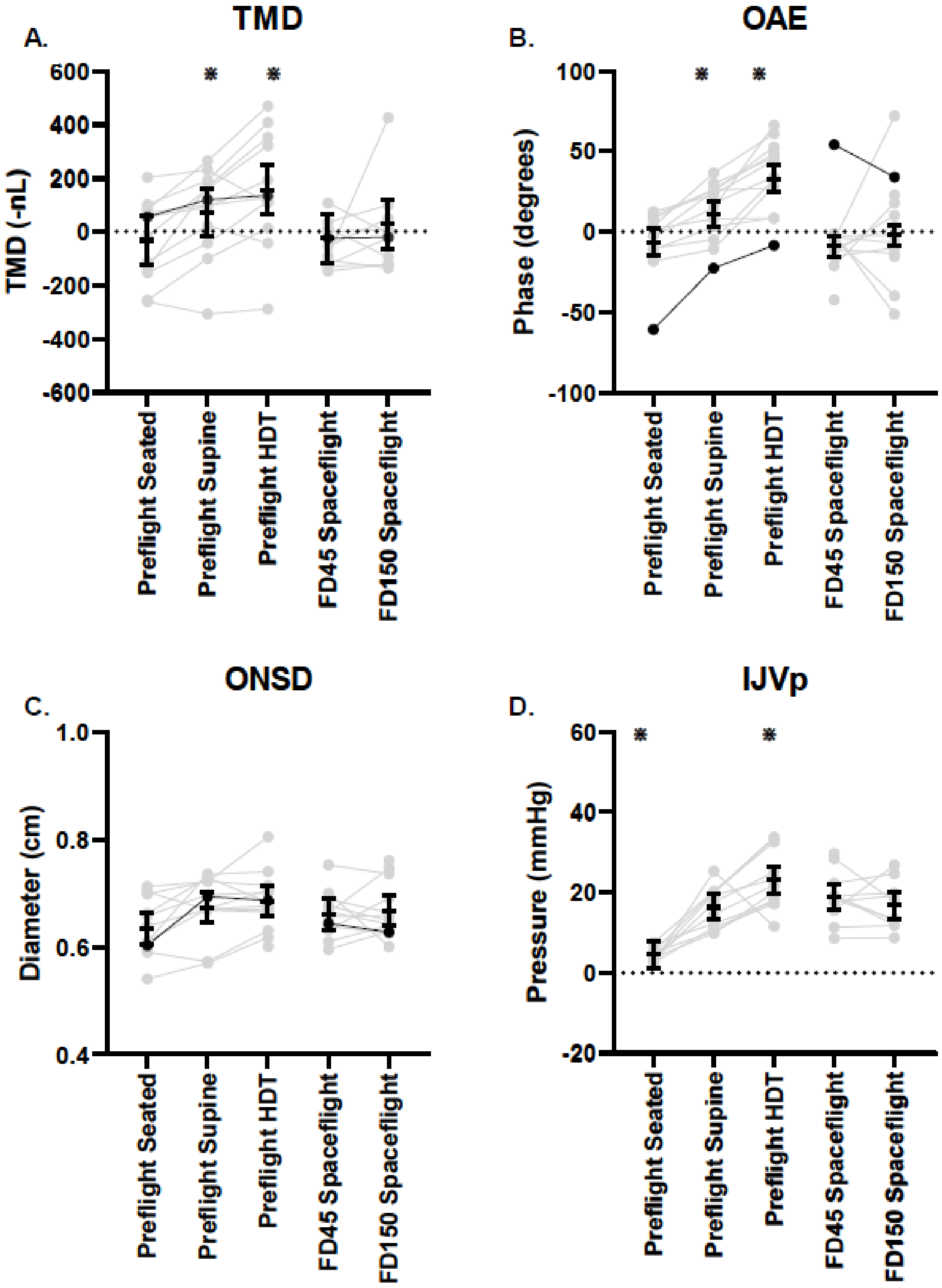
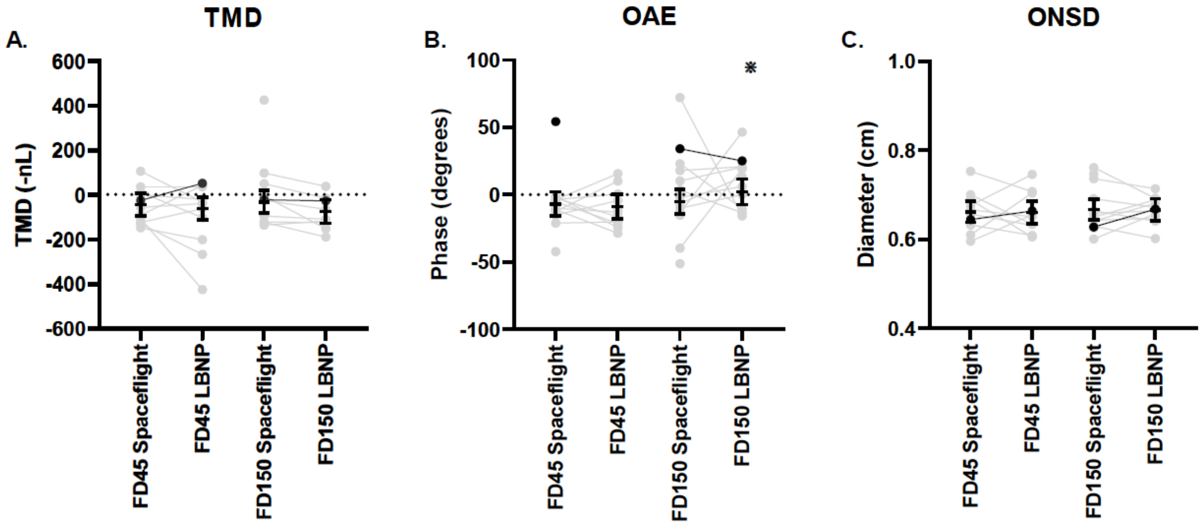

Preflight
Spaceflight
Postflight
Pre
FD45
FD150
R+10
R+30
R+180
Seated
Supine
15° HDT
(109±42 days)
Spaceflight
(44±9 days)
LBNP
(55±9 days)
Spaceflight
(142±25 days)
LBNP
(164±17 days)
Seated
Supine
15° HDT
(11±2 days)
Seated
Supine
15° HDT
(40±7 days)
Seated
Supine
15° HDT
(189±15 days)

Figure 2

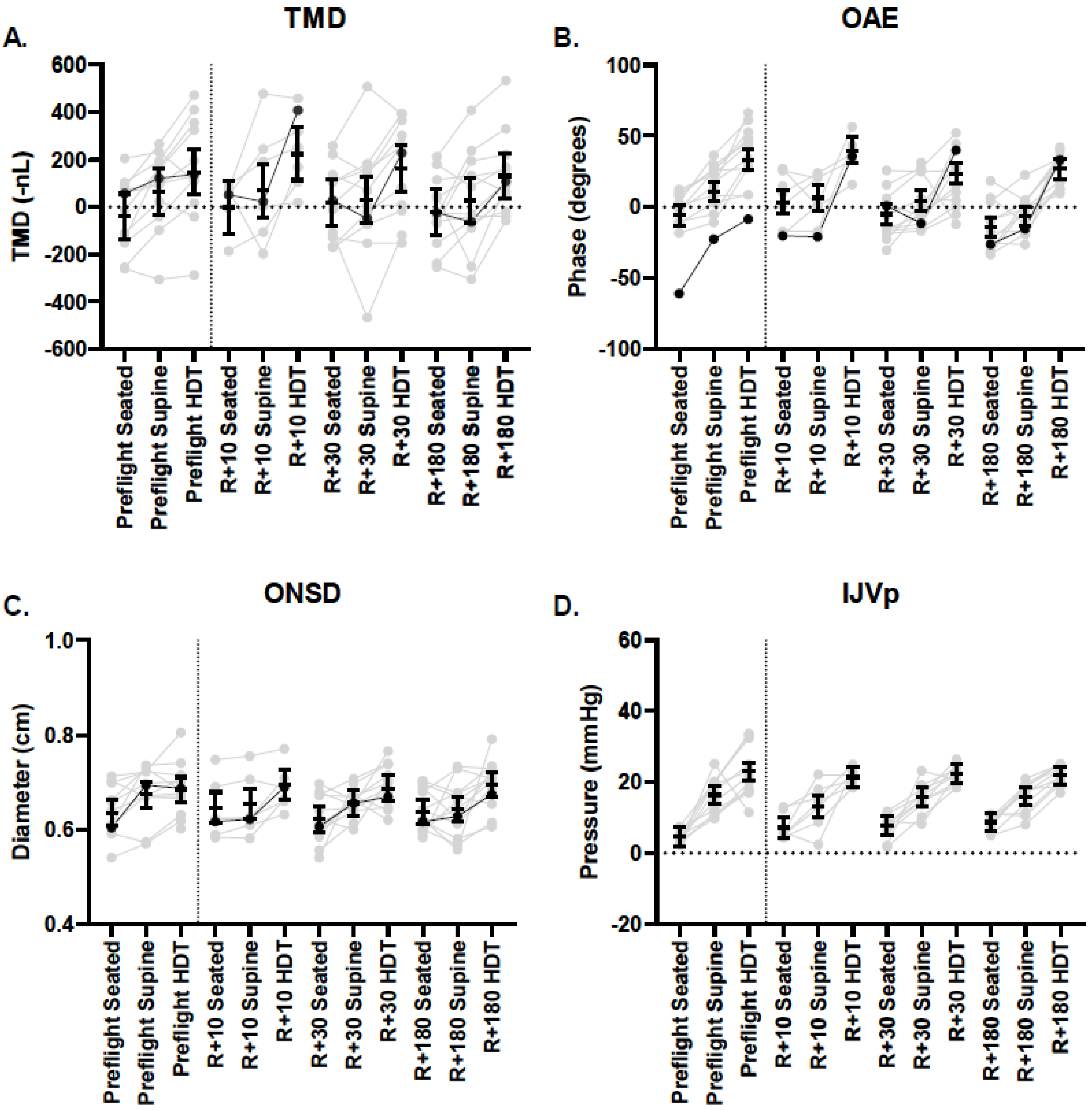

A.
TMD
TMD (-nL)
600
400
200
0
-200
-400
-600
*
*
B.
OAE
Phase (degrees)
100
50
0
-50
-100
*
*
C.
ONSD
Diameter (cm)
1.0
0.8
0.6
0.4
D.
IJVp
Pressure (mmHg)
60
40
20
0
-20
*
*
Preflight Seated
Preflight Supine
Preflight HDT
FD45 Spaceflight
FD150 Spaceflight

695 Figure 3



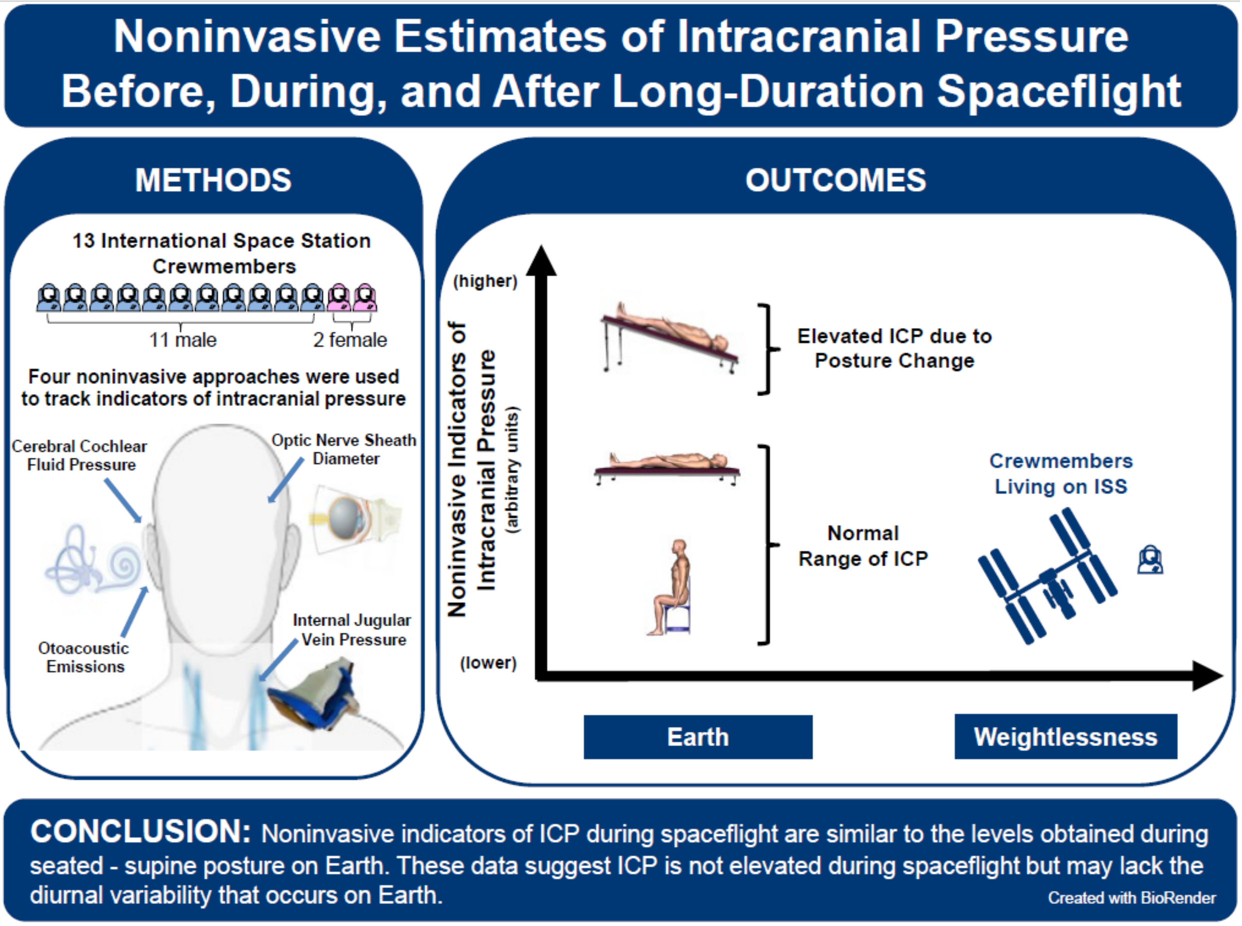
696

Figure 4



A.
TMD
TMD (-nL)
600
400
200
0
-200
-400
-600
B.
OAE
Phase (degrees)
100
50
0
-50
-100
C.
ONSD
Diameter (cm)
1.0
0.8
0.6
0.4
D.
IJVp
Pressure (mmHg)
60
40
20
0
-20
Preflight Seated
Preflight Supine
Preflight HDT
R+10 Seated
R+10 Supine
R+10 HDT
R+30 Seated
R+30 Supine
R+30 HDT
R+180 Seated
R+180 Supine
R+180 HDT

Graphical Abstract



Noninvasive Estimates of Intracranial Pressure Before, During, and After Long-Duration Spaceflight

METHODS

13 International Space Station Crewmembers

Four noninvasive approaches were used to track indicators of intracranial pressure

OUTCOMES

CONCLUSION: Noninvasive indicators of ICP during spaceflight are similar to the levels obtained during seated - supine posture on Earth. These data suggest ICP is not elevated during spaceflight but may lack the diurnal variability that occurs on Earth.

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