Increased Intraocular Pressure in Glaucomatous, Ocular Hypertensive, and Normotensive Space Shuttle Crew

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BACKGROUND: Glaucoma and ocular hypertension (OHT) are prevalent diseases with baseline intraocular pressure (IOP) elevations that future astronauts and spaceflight participants may suffer from. Preflight, in-flight, and postflight IOP measurements were collected aboard two U.S. Space Shuttle Program missions in normotensive control, OHT, and glaucomatous crewmembers.

METHODS: Five subjects (three controls, one glaucomatous, one OHT) were studied aboard 2-wk Space Shuttle missions. Baseline IOP (triplicate; handheld tonometry) was recorded during training 1–2 mo preflight, in flight (1–14 d), and postflight (3–29 d). Subjective symptoms were recorded via questionnaires. Data were analyzed using a spreadsheet with two-sample *t*-tests. *P*-value < 0.05 determined significance.

RESULTS: IOP increased for all in-flight vs. preflight measurements for controls ($N = 3$, +48.9%, +16.9%, +5.85%), OHT ($N = 1$, +20.3%), and glaucomatous ($N = 1$, +32.2%) groups. IOP eventually returned to baseline postflight [Return (R)+3–5 d], except for the astronaut with OHT (R+9–17). Subjective symptoms, likely multifactorial, included blurred vision, decreased visual acuity, and headaches.

DISCUSSION: IOP increased during spaceflight and normalized upon return. Astronauts and commercial spaceflight participants may need screening for elevated IOP to potentially prevent sequelae related to glaucoma and OHT, the former which requires treatment in flight and the latter which may need prophylaxis. Previous studies have shown elevated IOP upon entry into microgravity with various normalization timeframes in flight and postflight. It is unclear how increased IOP relates to spaceflight-associated neuro-ocular syndrome (SANS); however, several hypotheses exist. Treatment strategies should be available for acute and chronic ocular pathology during spaceflight despite the unique challenges of eye-drop application in microgravity.

KEYWORDS: glaucoma, ocular hypertension, spaceflight, intraocular pressure.

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Microgravity contributes to several physiological changes during spaceflight, which include loss of hydrostatic pressure within fluid columns (arterial, venous, cerebrospinal fluid, and lymphatics), reduced gravitational loading, diminished sensory input, and changes in transcapillary and lymphatic exchange systems.[19] These adverse effects manifest as adaptations in various organ systems in astronauts, including the cardiovascular, immune, musculoskeletal, and genitourinary systems.[19] Another area of involvement that has been extensively studied in the last decade is the visual system.

Spaceflight-associated neuro-ocular syndrome (SANS) represents a pathological maladaptation to microgravity that may persist upon return to Earth and may even be permanent.[9] Neuro-ophthalmic changes were more often seen in long-duration spaceflight. The most common symptom of SANS reported by crewmembers is decreased near-field visual acuity, due to a hyperopic shift. The physical manifestations are optic nerve protrusion, optic disc edema, posterior globe flattening, choroidal folds, and retrobulbar expansion of the optic nerve

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sheath.[13] Although the specific mechanism for SANS has not been determined, it is postulated that a cephalad fluid migration during microgravity causes intracranial and intraocular fluid shifts predisposing astronauts to SANS.[14] While multiple theories exist, one hypothesis is that a mismatch between intraocular pressure (IOP) and intracranial pressure (ICP) may contribute to optic nerve head remodeling and to the development of SANS.[20]

Intraocular pressure in microgravity was first measured by Draeger et al. in parabolic flight, noting a 5-mmHg average increase in IOP (N = unknown) using a hand-held applanation tonomoter.[4] In another parabolic flight study, IOP increased by 7 mmHg (58%, N = 11) within 20 s of weightlessness, measured with a Tono-Pen.[11] Preliminary studies in normal astronauts showed elevations in IOP in the first few hours into microgravity with normalization to baseline IOP values within 4 d in flight. In the German D1 Spacelab mission, IOP increased by 20–25% (N = 1) after 44 min of microgravity exposure followed by a decrease to baseline.[3] Similarly, on Soyuz TM-14 and D2 Spacelab, IOP increased by 92% (N = 1) and 114% (N = 2) within 15–16 min in flight followed by a return to baseline within 7 h 18 min and 3–4 d, respectively.[3] Finally, Shuttle data from six missions (N = 11) showed increases in IOP during flight day (FD) 1, with several measurements above the ocular hypertension threshold (21 mmHg) even as late as FD 9–10 with a return to baseline in flight or postflight.[16]

Glaucoma, which afflicts 2.1% of Americans over age 40, is a pathologically elevated baseline IOP (normal IOP = 8–21 mmHg) in patients who experience painless decreased peripheral vision and optic nerve cupping. It is most commonly treated with eye drops intended to lower IOP through several different pharmacological mechanisms. Ocular hypertension (OHT), which afflicts up to 9.4% of Americans over age 40, is an elevated baseline IOP without peripheral visual field loss or optic nerve changes.[10] Patients with OHT may eventually develop glaucoma. Typically, OHT patients are not treated and are followed up at regular intervals. However, OHT patients at increased risk for development of glaucoma may benefit from topical medications, typically initiated when two IOP measurements greater than 22–25 mmHg are recorded.[10,18] Both OHT and glaucoma are likely underdiagnosed due to the very gradual progression or the complete lack of symptoms. Future astronauts and spaceflight participants may have OHT or glaucoma. Studies of IOP in space are limited in number and investigation of IOP in subjects with OHT and glaucoma is altogether lacking despite potential implications for commercial spaceflight and long-duration mission crew. Even though spaceflight participants may only have minimal exposure to microgravity, this population has yet to be studied and it is unknown how even limited exposure may impact underlying conditions like OHT and glaucoma.

In this original investigation, we studied the impact of short-duration spaceflight on IOP changes in U.S. Space Shuttle Program crewmembers with OHT, glaucoma, and normotensive baseline pressures in the pre-, in-, and postflight periods. The study was conducted considering the opportune occurrence that astronauts with glaucoma and ocular hypertension were flying in space for the first time in spaceflight history. We hope to elucidate changes experienced in these two unstudied populations (OHT and glaucoma) and the potential implications for long-duration missions and commercial spaceflight.

METHODS

Subjects

Five subjects (three controls, one glaucomatous, one OHT), with a mixed subject population inclusive of both men and women, underwent the study aboard two 2-wk U.S. Space Shuttle Program missions. To ensure anonymity in this easily identifiable population, further description of the missions is omitted. After daily experiments and tasks were completed, the ancillary study was carried out to obtain IOP measurements. The experiment flight package, including all crew studies, was approved by the NASA Johnson Space Center Institutional Review Board.

Procedures

IOP measurements were obtained in the preflight (1–2 mo preflight), in-flight (within 1–4 d in flight and repeated at either 5–9 d or 10–14 d), and postflight (within 3–5 d postflight, 9–17 d, or 29+ d) periods. Triplicate IOP measurements were taken using the same handheld indentation tonometer (Tono-Pen XL Model #230,635, Reichert Technologies, Depew, NY, USA). For all crewmembers, IOP measurements were taken as close as possible within their busy mission schedules. Unfortunately, due to the nature of spaceflight missions, NASA requires all gear to be stowed months prior to flight. Consequently, we used different instruments for the in-flight period vs. the pre- and postflight periods, but ensured we used the same tonometer model. Preflight and postflight measurements were made in the seated position. Calibration verification of the tonometer on Earth was performed prior to each data session using the manufacturer recommended method: 1) turning the instrument vertical; 2) reversing the direction; and 3) monitoring for an instrument cue indicating verified calibration. While the tonometer was calibration verified before inclusion in the in-flight equipment, repeat calibration verification in space was not possible since this process is gravity dependent. Postflight, the in-flight tonometer was checked and verified as calibrated. For the glaucomatous crewmember, gonioscopy was performed preflight and the angle was determined to be open (not significantly narrow or closed). Additional equipment (e.g., gonioscopic lens, slit lamp, applanation tonometer) were not brought aboard the spacecraft given this study's ancillary role in the mission. Additionally, the weight of such extra equipment would be cost-prohibitive and would require an extensive process to remake the mission kits since ancillary testing was approved late in the mission planning timeline. Subjective symptoms were recorded via questionnaires, but objective measurements of changes other than IOP were not performed due to time constraints and lack of equipment (e.g., Snellen chart).

The subject with previously diagnosed primary open angle glaucoma had been successfully treated with timolol maleate (0.5%) for several years prior to flight. The crewmember had no history of glaucoma surgery or laser treatment. IOPs prior to treatment were unknown since the crewmember presented to NASA for preflight selection while already on treatment. While at NASA, timolol was continued with IOPs remaining between 15–19 mmHg. There was moderate cupping and healthy rim tissue indicating early or mild disease severity. The visual fields were normal and there was minimal retinal nerve fiber layer thinning. During the preflight period, this astronaut's medication was changed to a prostaglandin analog 3 mo prior to launch to gain an improved drug-safety profile, minimizing risk from potentially detrimental cardiopulmonary side effects of beta-blockers, albeit a low risk with topical ocular drop preparations.[15] The astronaut had no side effects with the prostaglandin analog during the 3-mo period leading up to the flight, and his IOPs were well-controlled. The subject used the medication at normal dose levels of one drop per day in flight. No missed doses were reported and the subject remained on the prostaglandin analog for years postflight.

Meanwhile, the subject with OHT did not use any medications during the study period. Given no documented IOPs greater than 21 mmHg and no progression to glaucoma, which would necessitate treatment, no medications were taken at baseline. Similarly, the three control subjects did not use medications.

Statistical Analysis

Triplicate IOP measurements were taken and average measurements for preflight, in flight, and postflight were used for statistical analyses. Percent changes in IOP in the previous three categories were calculated by comparing mean IOP measurements. Data were analyzed using Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA) using independent sample *t*-tests for the following comparisons of IOP: preflight to in-flight, in-flight to postflight, and preflight to postflight. Means (M) and SD are presented within the text and tables with *P*-values, *t* statistics, and degrees of freedom. Statistical significance was set at $\alpha = 0.05$. One-way ANOVA testing with Tukey's post hoc was completed as appropriate for further comparison of all flight periods for each subject. Subjective symptoms were assessed qualitatively and reported by number of crewmembers experiencing symptoms, including the specific symptomatology.

RESULTS

In all groups, IOP measurements increased during the first few days of spaceflight, stabilized, and subsequently decreased to baseline (preflight) values postflight. Normotensive crewmember 1 showed a 48.9% increase in IOP during FD 1–4 with a change from 11.9 mmHg to 17.7 mmHg [$t(6) = -5.490$, $P = 0.001529$, **Table I**]. Normotensive crewmember 2 showed a 16.9% increase in IOP during FD 1–4 with a change from 11.4 mmHg to 13.3 mmHg [$t(7) = -1.638$, $P = 0.145343$, Table I]. A 54.9% increase in IOP during FD 10–14 with a change from 11.4 mmHg preflight to 17.7 mmHg was also noted [$t(8) = -3.423$, $P = 0.009044$, Table I]. Normotensive crewmember 3 showed a 5.9% increase in IOP during FD 1–4 with a change from 14.9 mmHg to 15.8 mmHg [$t(2) = -0.347$, $P = 0.761436$, Table I]. All normotensive crewmembers returned to baseline IOP with no significant changes from pre- and postflight.

For the ocular hypertensive crewmember, IOP increased by 20.3% during FD 1–4 with a change from 18.2 mmHg to 21.9 mmHg [$t(23) = -2.135$, $P = 0.043636$]. IOP remained at 21.9 mmHg during flight then increased to 25.8 mmHg postflight (3–5 d), a 41.6% increase compared to preflight [$t(19) = -2.644$, $P = 0.016$]. IOP decreased to baseline (15.6 mmHg) postflight (9–17 d) (Table I). For the glaucomatous crewmember, IOP increased by 32.3% during FD 1–4 from 15.5 mmHg to 20.5 mmHg [$t(13) = -5.028$, $P = 0.000231$] and returned to baseline (17.0 mmHg) postflight (3–5 d) (Table I).

One-way ANOVA was supplementally considered for this study. Comparison of preflight, in-flight, and postflight intraocular pressures with one-way ANOVA showed significant differences for all crewmembers except normotensive crewmember 3 (**Table II**). Post hoc comparisons using the Tukey's HSD test detected significant differences in preflight vs. in-flight for normotensive crewmember 1, normotensive crewmember 3, and the glaucomatous crewmember. For the ocular hypertensive crewmember, significant differences were only detected between postflight (R+3–5) and postflight (R+9–17). No significant differences were detected for normotensive crewmember 3 (Table II).

The overall intraocular pressure trend for all crewmembers was an increase in IOP in flight followed by a return to baseline postflight. **Fig. 1** graphically depicts these trends observed in the different groups.

Table I. Mean Intraocular Pressure Measurements and Standard Deviations for Preflight, In Flight, and Postflight.

TIME	PREFLIGHT	IN FLIGHT (1–4 d)	IN FLIGHT (5–9 d)	IN FLIGHT (10–14 d)	POSTFLIGHT (3–5 d)	POSTFLIGHT (9–17 d)	POSTFLIGHT (29+ d)	INCREASE IN IOP % (PRE- VS. 1-4 IN FLIGHT)
Normotensive 1	11.86 (1.71)	17.67 (0.58)*	X	17.67 (0.58)	X	X	10.0 (1.00)	48.91%
Normotensive 2	11.40 (2.99)	13.33 (0.58)	X	17.67 (1.15)*	12.33 (1.53)	X	X	16.92% 54.91% (10–14 d in-flight)
Normotensive 3	14.96 (2.56)	15.83 (3.07)	X	X	14.16 (0.71)	X	X	5.85%
Ocular hypertensive (OHT)	18.24 (3.97)	21.94 (3.11)*	X	21.83 (2.59)	25.83 (4.00)*	15.67 (3.41)	X	20.32% 41.64% (3–5 d postflight)
Glaucomatous	15.50 (2.21)	20.50 (1.63)*	19.25 (5.23)	X	17.00 (1.41)	17.16 (0.94)	X	32.25%

Mean IOP in mmHg with SD [mean (SD)] are included. Increase in IOP% = preflight to 1–4 d in flight unless otherwise specified. * = Statistically significant (independent samples *t*-test, alpha = 0.05) intraocular pressure increases compared to preflight baseline. X = data not available.

Table II. Single Factor ANOVA and Post Hoc Tukey's HSD Results Per Subject.

SUBJECT	DF	*F* STATISTIC	*P*-VALUE	SIGNIFICANT TREATMENT PAIRS (TUKEY'S HSD)
Normotensive 1	3,11	39.958393	0.000003*	Preflight vs. In-Flight (1–4, 10–14); In-Flight (1–4, 10–14) vs. Postflight (29)
Normotensive 2	3,12	5.498506	0.013064*	Preflight vs. In-flight (10–14)
Normotensive 3	2,5	0.236353	0.797846	ANOVA H_0 rejected
OHT	4,28	4.015517	0.010688*	Postflight (3–5) vs. Postflight (9–17)
Glaucomatous	4,26	2.947685	0.039124*	Preflight vs. In-Flight (1–4)

OHT = ocular hypertensive; df = degrees of freedom (between groups, within groups).
* = Statistically significant (single factor ANOVA, alpha = 0.05).

Subjective symptoms included transient mild blurred vision and headaches in all test subjects. Given the ubiquitous and likely multifactorial nature of these symptoms among most astronauts, they could not be directly associated with a rise in IOP.

DISCUSSION

Overall, IOP increased in flight and returned to baseline postflight likely as a result of cephalad fluid shifts in microgravity. All normotensive crewmembers had increases in IOP in flight with return to baseline postflight likely due to Earth's gravity equilibrating internal fluid dynamics. The OHT crewmember had a significant increase in IOP in flight. However, IOP continued to increase postflight (R+3–5 d) from 21.8 mmHg to 25.8 mmHg, followed by a return to baseline during postflight days 9–17. This may be a phenomenon observed in OHTs in which IOP is difficult to quell in flight and postflight, requiring a longer equalization period back to baseline. Alternatively, measurement error may be implicated, although measurements were performed in triplicate. Our small sample ($N = 1$) limits definitive conclusions, but this finding warrants further investigation

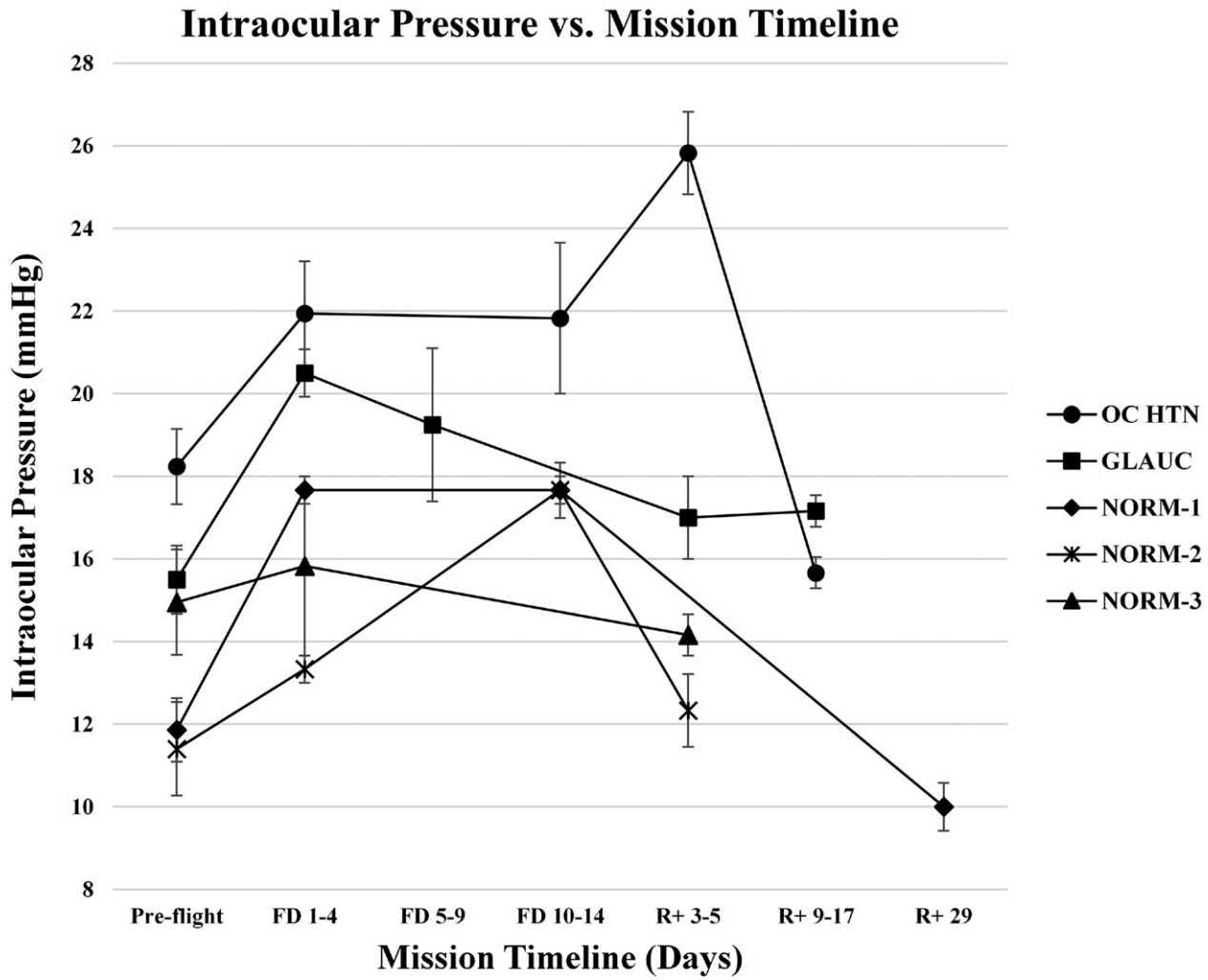

Fig. 1. Preflight, in-flight, and postflight mean intraocular pressure measurements with standard error for ocular normotensive crewmembers (NORM-1, NORM-2, and NORM-3), ocular hypertensive (OC HTN), and glaucomatous crewmembers (GLAUC). Flight day = FD; Return day = R+.

in this uniquely studied cohort. If such findings are repeatable in a larger sample size of patients with OHT, prophylactic eye drops may be warranted for OHT crewmembers to prevent significant increases in IOP and related sequalae like decreased peripheral vision if this exposure increases the risk of glaucoma.[17] Similarly, the glaucomatous crewmember also had a significant increase in IOP even with a continued treatment regimen. If such findings are consistent in future studies of larger cohorts, an increased dose and/or escalated regimen for glaucomatous crewmembers may be warranted during spaceflight to maintain IOP without significant increases, which could lead to worsening of visual fields and/or optic nerve damage.[12]

Astronaut candidates are rigorously screened for a variety of medical issues, including visual acuity and peripheral visual deficits. At the time of these flights, elevated IOP below 25, absence of glaucomatous optic nerve, and visual field changes were not disqualifying findings for astronaut selection.[5] If OHT or glaucoma developed postselection, medical exemptions were generally given for flight assignments if the condition was well managed with or without medications.[7] Future study is warranted to determine whether transient increases in IOP, particularly in patients with OHT or glaucoma, definitively contribute to the development of SANS and, if so, whether prophylactic treatment could decrease the incidence of pathological ocular changes during flight.[9,20]

Besides astronauts, another population under consideration for spaceflight includes spaceflight participants—those who have paid for a seat aboard commercial crew modules and spacecraft. Spaceflight participants do not undergo the rigorous astronaut selection process and may in fact have OHT or even glaucoma, both of which are commonplace in society.[7,10] Even though spaceflight participants would experience limited microgravity exposure, prior studies note large increases in IOP in parabolic flight and short duration spaceflight.[3,4,11,16] In crewmembers with normal IOP preflight, IOP changes in microgravity show a consistent initial rise within minutes of entry into microgravity and variability in the time course of return toward preflight pressures, with some returning to normal within a few hours to FD 2 and others showing elevated pressures up to FD 9–10, but almost all returning to preflight baseline IOPs by FD 30.[3,4,11,16] Researchers have suggested that an increase in episcleral venous pressure may normalize IOP in flight.[6] However, such a mechanism has not been studied in spaceflight. The ophthalmology literature notes that IOP increases in patients with OHT is a major risk factor for the development of primary open angle glaucoma. While these studies do not comment on the time interval of such increases, any increase is nevertheless a risk factor and should be addressed. Further studies may better identify the value of preflight OHT and glaucoma screening and the potential role of prophylactic treatment in high-risk individuals participating in commercial spaceflight.[17]

The subjective symptoms reported by the astronauts, while also important, are likely multifactorial in nature. Symptoms may also be attributed to cephalad fluid shifts and changes in the lens and globe, although we were unable to objectively measure these changes. Additionally, factors such as elevated carbon dioxide in spaceflight environments may also play a role in symptomology.[8] As such, there are limitations to what can be extrapolated by our subjective questionnaires.

This study also brings to light the difficulty of treating ocular conditions, which often require eye drops. Several astronauts have reported challenges with sterile administration of small volume liquids (eye drops) in microgravity. In preparation for the Shuttle missions above, flight surgeons, optometrists, and astronauts flew aboard a reduced-gravity aircraft (KC-135A) and demonstrated that capillary action can draw the expressed eye droplet when applied to the lateral canthus with the eye deviated in the opposite direction. While doing so allows for the medication to reach the eye surface, the process is still flawed. Issues include: 1) trauma to the eye (including corneal abrasion) from the medication applicator tip; 2) loss of dose control—an application of 8–10 drops equivalency with one in-flight application; 3) potential contamination of the eye-drop applicator touching the subject's lids/lashes; 4) potential cross contamination between subjects if the eye-drop applicator is shared given limited resources available in flight; and 5) potential adverse reactions consequent to systemic absorption of excessive amounts of pressure lowering medications like timolol maleate.[15]

There are several limitations to our study, most of which relate to the nature of conducting experiments in spaceflight. The most evident limitation is the small sample size ($N = 5$), with two experimental groups comprising one subject each ($N = 1$ glaucoma, $N = 1$ OHT). The onboard measurement of IOP is severely limited by the complexity and mass of traditional ophthalmic instruments, the extensive training required to operate and successfully conduct an examination using such instruments, restrictions to onboard mass and volume, and the difficulty of onboard medical studies, which are often relegated to convenience or opportunistic study design. Furthermore, IOP measurements were collected out of convenience for the astronauts' busy schedules, leading to inconsistent measurement flight dates/times. The timing of all measurements (preflight, in-flight, postflight) was not performed on the exact same day in all instances for the subjects in large part due to other NASA experiments or operations taking precedence. As such, diurnal variations in IOP, although different in microgravity than on the ground [$N = 1$, peak IOP at 19:00 (microgravity) vs. 07:00 (ground)], were not accounted for.[2] In addition, the Tono-Pen XL tonometer was not recalibrated in flight since this process is gravity dependent, potentially affecting sample collection. Whether microgravity perturbed the calibration is unknown, although postflight, the tonometer used in flight was verified as appropriately calibrated. On Earth, in a 1-gravitational (1-G) force environment, contact tonometers like the Tono-Pen are used in different axes toward the gravitational vector (upright vs. supine with a 0.9 ± 1.7 mmHg difference),[1] implying that the Tono-Pen XL is a gravity independent instrument.

Despite these limitations, the authors are unaware of prior studies of in-flight measurements of ocular pressure in astronauts with known history of OHT and glaucoma. For upcoming commercial flights with spaceflight participants, this study

provides valuable preliminary data to foster the development of additional studies involving IOP changes in microgravity and in prevention and treatment algorithms for any spaceflight participants identified to be at risk for ocular hypertension and glaucoma.

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