Title: Incidence and progression of chorioretinal folds during long-duration spaceflight

Authors:
Connor R. Ferguson, MS
Aegis Aerospace, Houston, TX

Laura P. Pardon, OD, PhD
KBR, Houston, TX

Steven S. Laurie, PhD
KBR, Houston, TX

Millennia H. Young, PhD
NASA Johnson Space Center, Houston, TX

C. Robert Gibson, OD
KBR, Houston, TX
South Shore Eye Center, League City, TX

Tyson J. Brunstetter, OD, PhD
NASA Johnson Space Center, Houston, TX

William J. Tarver, MD
NASA Johnson Space Center, Houston, TX

Sara S. Mason, MS
Aegis Aerospace, Houston, TX

Patrick A. Sibony, MD
Department of Ophthalmology, Stony Brook Medicine, Stony Brook, NY

[1]Brandon R. Macias, PhD
NASA Johnson Space Center, 2101 NASA Pkwy, Mail Code SK3, Houston, TX 77058
brandon.r.macias@nasa.gov

Word Count: 2996

[1]Corresponding author

Key Points

Question: What is the incidence, presentation, and progression of chorioretinal fold development during long-duration spaceflight missions to the International Space Station (ISS)?

Findings: In this retrospective analysis of 36 long-duration crewmembers, 17% developed chorioretinal folds; presentation of folds in crewmembers differed from that reported in patients with idiopathic intracranial hypertension. Quantitative analysis revealed that the earliest appearance of choroidal folds varied among individuals and that both macular and peripapillary choroidal folds worsened with flight durations up to 1 year.

Meaning: Chorioretinal fold progression is a concern for present ISS missions and future longer-duration exploration missions to the Moon and Mars.

ABSTRACT

Importance: The primary contributing factor for development of chorioretinal folds during spaceflight is unknown. Characterizing fold types that develop and tracking their progression may provide insight into the pathophysiology of spaceflight-associated neuro-ocular syndrome and elucidate the risk of fold progression for future exploration-class missions exceeding 12 months in duration.

Objective: To determine the incidence and presentation of chorioretinal folds in long-duration International Space Station crewmembers and objectively quantify the progression of choroidal folds during spaceflight.

Design: In this retrospective cohort study, optical coherence tomography scans of the optic nerve head and macula were obtained on Earth prior to spaceflight and during flight. A panel of experts examined the scans for the qualitative presence of chorioretinal folds. Peripapillary total retinal thickness was calculated to identify eyes with optic disc edema, and choroidal folds were quantified based on surface roughness within macular and peripapillary regions of interest.

Setting: Before and during spaceflight missions to the International Space Station

Participants: 36 crewmembers completing long-duration spaceflight missions

Intervention(s) or Exposure(s): Spaceflight missions ranging 6-12 months

Main Outcomes and Measures: Incidence of peripapillary wrinkles, retinal folds, and choroidal folds; peripapillary total retinal thickness; Bruch's membrane surface roughness.

Results: Chorioretinal folds were observed in 12/72 eyes (17%; 6 crewmembers). In eyes with early signs of disc edema, 10/42 (24%) had choroidal folds, 4/42 (10%) had inner retinal folds, and 2/42 (5%) had peripapillary wrinkles. Choroidal folds were observed in all eyes with retinal folds and peripapillary wrinkles. Macular choroidal folds developed in 7 of the 12 eyes (4/6 crewmembers) with folds and progressed with mission duration; these folds extended towards the foveal region in 6 eyes. Circumpapillary choroidal folds developed predominantly superior, nasal, and inferior to the optic nerve head and increased in prevalence and severity with mission duration.

Conclusions and Relevance: Choroidal folds were the most common fold type to develop during spaceflight; this differs from reports in idiopathic intracranial hypertension, suggesting differences in the mechanisms underlying fold formation. Quantitative measures demonstrate the development and progression of choroidal folds during weightlessness, and these metrics may help to assess the efficacy of spaceflight-associated neuro-ocular syndrome countermeasures.

INTRODUCTION

Spaceflight-associated neuro-ocular Syndrome (SANS) was first described in a case series with five of seven astronauts presenting with optic disc edema and five of seven with choroidal folds after return from long-duration missions to the International Space Station (ISS).[1] Following these initial findings, additional reports documented development of retinal and choroidal folds during spaceflight and their persistence after return to Earth,[2–4] including a retrospective analysis that identified signs of choroidal folds in six of 15 (40%) participants.[5] Subsequently, quantitative evidence from optical coherence tomography (OCT) images revealed development and progression of optic disc edema in ~70% of ISS crewmembers flying 6-month missions[6] and that choroidal folds progressively worsened during a 1-year spaceflight mission in a single crewmember with Frisén grade 1 optic disc edema.[7] Development of chorioretinal folds at or near the macula has the potential to affect vision during spaceflight and impact visual function late in life if not resolved, yet the primary factor contributing to development and progression of chorioretinal folds remains unclear.

Folds are not common in terrestrial pathologies, but have been associated with acquired hyperopia, hypotony, ocular inflammatory disorders, and intracranial hypertension.[8–12] Prior to each mission, crewmembers undergo examinations to rule out inflammatory disorders, systemic disease, abnormal intraocular pressure (IOP), and use of medication that could produce intracranial hypertension. On rare occasions, low IOP can lead to choroidal folds, for example following surgery;[13] however, evidence suggests IOP is not decreased during long-duration spaceflight.[14,15] The presence of choroidal folds, retinal folds, or peripapillary wrinkles in terrestrial patients with optic disc edema may indicate elevated intracranial pressure (ICP) when other known causes such as orbital disease, tumor, posterior scleritis, and hypotony are ruled out.[16,17]

Folds develop within the retina due to changes in mechanical loading conditions and biomechanical tissue properties.[8,18] Thus, the timing, location, orientation, and pattern of fold presentation within the retina may provide insight into the underlying pathophysiology.[8,10,18,19] OCT imaging enables 3D visualization and quantification of fold morphology as compared to more traditional forms of ophthalmic imaging, and has led to the classification of choroidal folds, outer retinal folds and creases, inner retinal folds, and peripapillary wrinkles in patients with papilledema resulting from IIH.[10,20] The purpose of this study was to objectively document and quantify the prevalence and progression of choroidal folds, retinal folds, and peripapillary wrinkles in crewmembers flying long-duration spaceflight missions to the ISS. We hypothesized that the prevalence of chorioretinal folds in ISS crewmembers with optic disc edema would be similar in proportion to previous reports in IIH patients and that folds would worsen with greater spaceflight mission duration.

METHODS

Thirty-six crewmembers (seven female), including astronauts and cosmonauts, participated in spaceflight missions with mean (±SD) duration of 189 (±60) days onboard the ISS. Data were obtained during research studies approved by the NASA Johnson Space Center Institutional Review and Human Research Multilateral Review Boards. Participants provided written informed consent consistent with the Declaration of Helsinki and did not receive a stipend or incentives to participate. STROBE reporting guidelines were followed except reporting of study dates due to attributability concerns.

Bilateral OCT images were acquired with Spectralis OCT1 or OCT2 systems (Heidelberg Engineering, Heidelberg, Germany) before, during, and after long-duration spaceflight.[6] For crewmembers with prior spaceflight experience only images from the most recent spaceflight mission were analyzed. While scan placement was consistent within each individual before, during, and after spaceflight and across all crewmembers in this cohort, scan density and size were updated as the Spectralis OCT2 system became available for use on the ISS. All participants were imaged with a circle pattern (3.5 mm or 12°, 100 automatic real-time tracking levels [ART]) centered over the optic nerve head (ONH). Crewmembers were scanned with a 20°, 12-line, 16 ART (OCT1) or a 15°, 48-line, 25 ART (OCT2) radial scan pattern centered over the ONH. Similarly, a 20° x 20° (6 x 6 mm) vertical raster scan pattern centered on the fovea was acquired using a 25-line, 16 ART (OCT1) or 193-line, 16 ART (OCT2) pattern.

Automated segmentations of the internal limiting membrane (ILM), retinal nerve fiber layer (RNFL), and Bruch's membrane were manually corrected, verified by an additional expert grader, and processed in MATLAB (MathWorks, Natick, MA). Global peripapillary total retinal thickness (TRT) was calculated from the radial scans in an annular zone circumscribing the ONH within 250 μm of Bruch's membrane opening (BMO).[5,6] The choroidal-scleral interface was manually delineated on circular scans. Mean RNFL and choroid thickness were calculated from the circle scan pattern except in one crewmember with poor scan quality.[6,21] A panel of four experts (TJB, CRG, SSL, SSM) jointly inspected all OCT images for peripapillary wrinkles, retinal folds, and choroidal folds, following the classification criteria in the OCT Substudy of the Idiopathic Intracranial Hypertension Treatment Trial[10,20] and arrived at a consensus for each scan. The prevalence of chorioretinal folds in ISS crewmember eyes demonstrating optic disc edema based on TRT increase ≥ 19.4 μm[21] was compared to the previously reported prevalence of folds in IIH patients with papilledema.[10,20]

Surface roughness quantification improves on the peak shape analysis methodology previously reported in one ISS crewmember completing a one-year spaceflight mission.[7] Due to the limited number of crewmembers who developed folds during spaceflight and the greater prevalence of choroidal folds in the spaceflight cohort relative to peripapillary wrinkles and retinal folds, surface roughness data are presented for Bruch's membrane only. Bruch's membrane surface layer was aligned to a reference plane using singular value decomposition and polynomial curve fitting to remove scan tilt and curvature. The aligned surface layer was used to generate a topographical heightmap to aid visualization of the pattern and orientation of choroidal folds (Figure 1).

Bruch's membrane root mean square surface roughness[22] was measured in three adjacent 1x5 mm rectangular regions of interest (ROI) on the vertical raster scan pattern (Figure 1C). To measure progression of macular choroidal folds toward the fovea, the first and second rectangular ROIs were located between the fovea and ONH (Figure 1C, Fovea – 2 mm and Fovea – 1 mm). The third ROI was centered on the fovea (Figure 1C, Fovea). One crewmember who developed macular choroidal folds in the right eye during spaceflight was scanned with a 20° x 10° (6 x 3 mm) raster pattern which limited coverage to the Fovea – 1 mm and Fovea ROIs. In two crewmembers scanned with the 193-line 20° x 20° (6 x 6 mm) vertical raster pattern, a subset of 38 equally spaced lines of the 193 total lines were analyzed. Using the ONH radial scan pattern, the change in peripapillary Bruch's membrane surface roughness was measured within the superior, temporal, nasal, and inferior quadrants of an annular region corresponding to BMO + 500 to 1000 μm (Figure 1D).

Surface roughness precision testing was performed on a separate cohort of novice astronauts with normal healthy retinas studied in Laurie et al.[21] The statistical distribution of these measures was modeled with a Bayesian hierarchical model incorporating random effects for each source of variation (individual, session, analyzer, residual error) following previously published methodology used for precision analysis of TRT and choroidal thickness change.[21] Under the assumption of a normal test-retest distribution, a change in surface roughness within a peripapillary or macular ROI of more than 2.8 or 2.3 µm respectively (two standard deviations) would have a less than 5% chance of being observed due to sampling error or normal physiological variability. Therefore, a change in surface roughness greater than these values would be considered evidence of new or progressed fold.

RESULTS

Six of 36 crewmembers demonstrated at least one type of fold during spaceflight (12 of 72 study eyes, 17% incidence). Bilateral choroidal folds were identified in all six crewmembers. One of the six crewmembers presented with bilateral peripapillary and macular choroidal folds before the present spaceflight mission. Examples of choroidal folds, inner retinal folds, peripapillary wrinkles, and the distribution within this cohort are shown in Figure 2. There was no meaningful difference in age (P = .09), body mass index (P = .12), or mission duration (P = .11) between crewmembers that developed or did not develop folds (Table 1). Two of 36 crewmembers, both within the folds group, were diagnosed with bilateral Frisén grade 1 optic disc edema based on fundus photography. Optic disc edema assessed by an increase in TRT ≥ 19.4 µm[21] was observed in 25 of 36 (69%) crewmembers or 42 of 72 study eyes (58%). The folds group demonstrated a greater change in global peripapillary TRT (P = .03) and circumpapillary RNFL thickness (P = .03) during spaceflight than those without folds (Table 1).

The increase in global choroid thickness that developed during weightlessness was not different between groups (P = .81).

The prevalence of fold type observed in the subset of 42 spaceflight study eyes that demonstrated the earliest signs of optic disc edema (change in TRT ≥ 19.4 µm) was compared to the prevalence of fold type reported in the IIH Treatment Trial[10,20] (Figure 2D). One crewmember who developed bilateral choroidal folds during this spaceflight mission did not develop edema by any definition and was excluded from this comparison. Choroidal folds were most common in ISS crewmembers (24%) but were the least common fold type in IIH patients (10%).[10] Conversely, inner retinal folds and peripapillary wrinkles were observed least often in ISS crewmembers (10% and 5%, respectively) but were the most common fold type observed in IIH patients (46% and 46%, respectively).[10] Outer retinal folds were present in 20% of IIH patients[20] but were not observed in ISS crewmembers. In the two crewmembers with Frisén grade 1 optic disc edema and chorioretinal folds, lumbar puncture (LP) opening pressure measured 22 cmH_2O seven days postflight[23] and 19.4 cmH_2O nine days postflight respectively.

Macular choroidal folds were observed in seven study eyes of four crewmembers during spaceflight. One of the four crewmembers demonstrated bilateral macular choroidal folds before the present mission, a finding that was attributed to previous long-duration spaceflight. In all seven eyes with macular choroidal folds, Bruch's membrane surface roughness increased in the macular region as mission duration progressed (Figure 3). An increase in surface roughness at flight day (FD) 26 in the Fovea-2mm and Fovea-1mm region of interest preceded the increase in the Fovea sector between FD26 and FD63 in one eye from one crewmember (Figure 3: right eye, open square). One crewmember demonstrated a meaningful increase in surface roughness (+4.8 µm) in the Fovea - 2mm sector of their right eye between FD160 and FD266 while there was no change in the Fovea - 1mm and Fovea sectors (Figure 3: right eye, open triangle). The crewmember with pre-existing bilateral macular choroidal folds demonstrated a meaningful increase in surface roughness in the Fovea sector between FD28 and FD83 in both the right (+2.8 µm) and left (+4.9 µm) eye (Figure 3: Fovea, circles).

Peripapillary choroidal folds were observed bilaterally in all six crewmembers, though severity was variable between eyes within each crewmember (Figure 4, eFigure 1). In eight of twelve eyes with folds, peripapillary surface roughness increased during spaceflight within the nasal, superior, and inferior sectors, ranging from +2.8 to +13.4 µm, while minimal changes were observed in the temporal sector (Figure 4). In the right eye of one subject (Figure 4: open diamond), choroidal folds that began in the superior quadrant progressed to the temporal region after 120 days of spaceflight (+3.9 µm) and persisted for the remainder of the mission.

DISCUSSION

This report documents choroidal folds as the most common type of fold to develop during long-duration spaceflight in ISS crewmembers, occurring more than twice as frequently as retinal folds and peripapillary wrinkles. This finding contrasts with the distribution of fold types observed in IIH patients, suggesting the underlying mechanism(s) causing folds differs between these populations. Macular and peripapillary choroidal folds developed as early as FD26 and as late as FD266, and continued to worsen throughout 6-12 months of spaceflight. Progression of macular folds within the foveal region is of particular concern due to the potential to disrupt vision.

Peripapillary TRT increased more in crewmembers with folds, suggesting magnitude of optic disc edema may be associated with development of folds or wrinkles. However, it remains to be determined if edema is the primary contributing factor. In one crewmember, choroidal fold development without a meaningful increase in TRT may indicate involvement of other mechanisms, likely associated with the spaceflight-induced headward fluid shift and venous congestion. While choroidal engorgement may contribute to the development of folds, we observed a similar increase in choroid thickness in eyes with or without chorioretinal folds. In some eyes localized choroidal expansion coincided with structural changes in Bruch's membrane layer (supplemental eFigure 2), but the association of these observations requires further investigation.

Overlapping signs with IIH, including optic disc edema, chorioretinal folds, and globe flattening, led to the hypothesis that pathologically elevated ICP may have been the primary contributing factor to SANS.[1] However, direct measurements of ICP during brief periods of weightlessness induced by parabolic flight[24] and non-invasive estimates during spaceflight[23] suggest ICP does not reach levels observed in terrestrial pathologies such as IIH. In the initial report of eye changes after long-duration spaceflight,[1] one of two crewmembers without folds had a LP opening pressure of 21 cmH_2O at 19 days after return to Earth, while three of five with folds demonstrated pressures of 28, 28.5, and 22 cmH_2O at 12, 57, and 66 days after return to Earth, respectively. In the current study two additional crewmembers with chorioretinal folds had a LP opening pressure of 22[23] and 19.4 cmH_2O at seven and nine days after return to Earth, respectively. Mild chronic elevation of ICP throughout long-duration spaceflight could be sufficient to contribute to the development of chorioretinal folds, but further investigation during spaceflight is needed to determine the role of ICP in individual SANS cases.

If increased ICP were the primary factor influencing the development of chorioretinal folds in spaceflight, individuals with SANS and IIH might presumably have similar proportions of each fold type. The reduced frequency of peripapillary wrinkle and retinal fold development in SANS compared to IIH could be explained by the relatively mild level of disc edema that develops in most individuals during spaceflight. However, peripapillary wrinkles and inner retinal folds are more common than choroidal folds in strict head-down tilt bed rest where the magnitude of optic disc edema is comparable to spaceflight.[25] While folds in IIH may predominantly result from mechanical indentation due to elevated ICP,[1,10] effects of the headward fluid shift and venous congestion associated with spaceflight may alter the loading conditions of ocular structures in SANS.[23,26,27] Globe flattening at the ONH,[28] decreased axial length and hyperopic shift,[6] choroidal expansion,[6,14] and interstitial edema[26] may contribute to choroidal fold formation during spaceflight, although the magnitude of each individual contribution is unclear.

Data collected before the development of SANS provides unique insights not typically afforded in terrestrial patients with folds. Surface roughness quantification provides the ability to detect development of choroidal folds and objectively measure their progression. Analyses presented here demonstrate choroidal fold development as early as 26 days in weightlessness and continued progression throughout mission durations up to one year in both peripapillary and macular regions. Fold pattern schematics (supplemental eFigure 1) indicate similar presentation of choroidal folds among crewmembers: concentric, circumpapillary folds in the superior, nasal, and/or inferior quadrants accompanied by horizontal linear choroidal folds extending from the temporal periphery of the optic nerve head into the macula. This pattern may reflect asymmetric shape deformation in SANS consistent with radial mechanical compression of Bruch’s membrane layer nasal, and tension temporal to the ONH.

Macular choroidal folds directly involved the fovea in six eyes from four crewmembers (supplemental eFigure1). Despite these structural changes, each of the four crewmembers demonstrated best corrected visual acuity of 20/15 or better with normal visual fields and Amsler grid findings within four days postflight. However, disruption of the foveal photoreceptor layer could pose a vision concern for future extended-duration missions. Choroidal folds have been reported to persist > 5 years postflight in some crewmembers[1,4] and long-term effects on ocular health and vision remain to be fully explored. Bruch's membrane surface roughness quantification could present an objective approach to predict a threshold of deformation past which folds do not fully resolve after return to Earth.

While most long-duration ISS crewmembers are affected by early signs of disc edema,[6,29] a smaller proportion develop chorioretinal folds (17% in this cohort). In this study, there was no consistent bias in development or progression of folds for the right or left eye, or in either sex. Individual anatomical differences, for example in choroidal anatomy, may play a role in the development of choroidal folds.[1,8] Although two of the six crewmembers with folds documented in this report were novice fliers, cumulative effects of optic disc edema, choroidal expansion, and globe flattening across repeated long-duration spaceflight missions may alter mechanical properties of the ONH and retina and increase propensity for structural change. Quantitative monitoring of choroidal folds, retinal folds, and peripapillary wrinkles will help characterize vision risk on future exploration-class missions.

LIMITATIONS

While this study reflects the available evidence to date, the total number of subjects is small and requires future research to confirm these findings. Interpretation of the results presented could have been influenced by the orientation of available scans relative to the orientation of the folds being measured; however, the number of scans used in this analysis should provide sufficient resolution to minimize this source of error.

CONCLUSIONS

We present a novel approach to objectively track choroidal fold development and demonstrate continued worsening of folds throughout spaceflight missions up to one year in duration. Differences in prevalence of fold types between SANS and IIH provides further evidence that elevated ICP is not likely the sole contributing factor to choroidal fold development during spaceflight. Quantitative measures provide a sensitive method for detecting and tracking folds over time and may highlight a vision concern for extended exploration missions. Future applications of the surface roughness metric should be considered to assess efficacy of SANS countermeasures.

ACKNOWLEDGMENTS

We thank the crewmembers who participated in this research, members of the Cardiovascular and Vision Laboratory for their assistance with OCT segmentation and technical support, supporting elements of NASA's Human Research Program, and international partners. This study was directed research supported by NASA's Human Research Program. The funding agency did not have a role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. None of the authors have any conflicts of interest or financial disclosures. CRF and BRM had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. CRF (Aegis Aerospace), LPP (KBR), and MHY (NASA) conducted and are responsible for the data analysis.

REFERENCES

1. Mader TH, Gibson CR, Pass AF, et al. Optic disc edema, globe flattening, choroidal folds, and hyperopic shifts observed in astronauts after long-duration space flight. *Ophthalmology*. 2011;118(10):2058-2069. doi:10.1016/j.ophtha.2011.06.021

2. Mader TH, Gibson CR, Barratt MR, et al. Persistent globe flattening in astronauts following long-duration spaceflight. *Neuroophthalmology*. 2021;45(1):29-35. doi:10.1080/01658107.2020.1791189

3. Mader TH, Gibson CR, Pass AF, et al. Optic disc edema in an astronaut after repeat long-duration space flight. *J Neuro-Ophthalmol*. 2013;33(3):249-255. doi:10.1097/WNO.0b013e31829b41a6

4. Mader TH, Gibson CR, Otto CA, et al. Persistent Asymmetric Optic Disc Swelling After Long-Duration Space Flight: Implications for Pathogenesis. *J Neuroophthalmol*. Published online December 5, 2016. doi:10.1097/WNO.0000000000000467

5. Patel N, Pass A, Mason S, Gibson CR, Otto C. Optical coherence tomography analysis of the optic nerve head and surrounding structures in long-duration International Space Station astronauts. *JAMA Ophthalmol*. 2018;136(2):193-200. doi:10.1001/jamaophthalmol.2017.6226

6. Macias BR, Patel NB, Gibson CR, et al. Association of Long-Duration Spaceflight With Anterior and Posterior Ocular Structure Changes in Astronauts and Their Recovery. *JAMA Ophthalmol*. 2020;138(5):553-559. doi:10.1001/jamaophthalmol.2020.0673

7. Macias BR, Ferguson CR, Patel N, et al. Changes in the optic nerve head and choroid over 1 year of spaceflight. *JAMA Ophthalmol*. 2021;139(6):663-667. doi:10.1001/jamaophthalmol.2021.0931

8. Friberg TR. The etiology of choroidal folds. A biomechanical explanation. *Graefes Arch Clin Exp Ophthalmol*. 1989;227(5):459-464. doi:10.1007/BF02172899

9. Grosso D, Borrelli E, Sacconi R, Bandello F, Querques G. Recognition, Diagnosis and Treatment of Chorioretinal Folds: Current Perspectives. *Clin Ophthalmol*. 2020;14:3403-3409. doi:10.2147/OPTH.S241002

10. Sibony PA, Kupersmith MJ, Feldon SE, Wang JK, Garvin M, OCT Substudy Group for the NORDIC Idiopathic Intracranial Hypertension Treatment Trial. Retinal and choroidal folds in papilledema. *Invest Ophthalmol Vis Sci*. 2015;56(10):5670-5680. doi:10.1167/iovs.15-17459

11. Cassidy LM, Sanders MD. Choroidal folds and papilloedema. *British Journal of Ophthalmology*. 1999;83(10):1139-1143. doi:10.1136/bjo.83.10.1139

12. Murdoch D, Merriman M. Acquired hyperopia with choroidal folds: Acquired hyperopia with choroidal folds. *Clinical & Experimental Ophthalmology*. 2002;30(4):292-294. doi:10.1046/j.1442-9071.2002.00536.x

13. Williams BK, Chang JS, Flynn HW. Optical coherence tomography imaging of chorioretinal folds associated with hypotony maculopathy following pars plana vitrectomy. *Int Med Case Rep J*. 2015;8:199-203. doi:10.2147/IMCRJ.S86143

14. Greenwald SH, Macias BR, Lee SMC, et al. Intraocular pressure and choroidal thickness respond differently to lower body negative pressure during spaceflight. *J Appl Physiol (1985)*. 2021;131(2):613-620. doi:10.1152/japplphysiol.01040.2020

15. Draeger J, Schwartz R, Groenhoff S, Stern C. Self-tonometry under microgravity conditions. *Aviat Space Environ Med*. 1995;66(6):568-570.

16. Carta A, Favilla S, Prato M, Bianchi-Marzoli S, Sadun AA, Mora P. Accuracy of Funduscopy to Identify True Edema versus Pseudoedema of the Optic Disc. *Invest Ophthalmol Vis Sci*. 2012;53(1):1. doi:10.1167/iovs.11-8082

17. Reggie SN, Avery RA, Bavinger JC, et al. The sensitivity and specificity of retinal and choroidal folds to distinguish between mild papilloedema and pseudopapilledema. *Eye*. Published online January 19, 2021. doi:10.1038/s41433-020-01368-y

18. Del Priore LV. Stiffness of Retinal and Choroidal Tissue: A Surface Wrinkling Analysis of Epiretinal Membranes and Choroidal Folds. *American Journal of Ophthalmology*. 2006;142(3):435-440.e1. doi:10.1016/j.ajo.2006.04.019

19. Sibony PA. Gaze Evoked Deformations of the Peripapillary Retina in Papilledema and Ischemic Optic Neuropathy. *Invest Ophthalmol Vis Sci*. 2016;57(11):4979-4987. doi:10.1167/iovs.16-19931

20. Sibony PA, Kupersmith MJ. “Paton’s Folds” Revisited: Peripapillary Wrinkles, Folds, and Creases in Papilledema. *Ophthalmology*. 2016;123(6):1397-1399. doi:10.1016/j.ophtha.2015.12.017

21. Laurie SS, Lee SMC, Macias BR, et al. Optic disc edema and choroidal engorgement in astronauts during spaceflight and individuals exposed to bed rest. *JAMA Ophthalmol*. 2020;138(2):165-172. doi:10.1001/jamaophthalmol.2019.5261

22. Black JT, Kosher RA. Chapter 37: Surface Engineering. In: *Degarmo’s Materials and Processes in Manufacturing*. 11th ed. John Wiley & Sons, Inc.; 2012:1030-1036.

23. Jasien JV, Laurie SS, Lee SMC, et al. Noninvasive indicators of intracranial pressure before, during, and after long-duration spaceflight. *Journal of Applied Physiology*. 2022;133(3):721-731. doi:10.1152/japplphysiol.00625.2021

24. Lawley JS, Petersen LG, Howden EJ, et al. Effect of gravity and microgravity on intracranial pressure. *J Physiol (Lond)*. 2017;595(6):2115-2127. doi:10.1113/JP273557

25. Laurie SS, Greenwald SH, Marshall-Goebel K, et al. Optic disc edema and chorioretinal folds develop during strict 6° head-down tilt bed rest with or without artificial gravity. *Physiol Rep*. 2021;9(15):e14977. doi:10.14814/phy2.14977

26. Stenger MB, Laurie SS, Sadda SR, Sadun AA, Macias BR, Huang AS. Focus on the optic nerve head in spaceflight-associated neuro-ocular syndrome. *Ophthalmology*. 2019;126(12):1604-1606. doi:10.1016/j.ophtha.2019.09.009

27. Feola AJ, Nelson ES, Myers J, Ethier CR, Samuels BC. The impact of choroidal swelling on optic nerve head deformation. *Invest Ophthalmol Vis Sci*. 2018;59(10):4172-4181. doi:10.1167/iovs.18-24463

28. Sater SH, Sass AM, Rohr JJ, et al. Automated MRI-based quantification of posterior ocular globe flattening and recovery after long-duration spaceflight. *Eye*. Published online January 29, 2021:1-10. doi:10.1038/s41433-021-01408-1

29. Pardon LP, Macias BR, Ferguson CR, et al. Changes in Optic Nerve Head and Retinal Morphology During Spaceflight and Acute Fluid Shift Reversal. *JAMA Ophthalmol*. 2022;140(8):763-770. doi:10.1001/jamaophthalmol.2022.1946

TABLES

Table 1. ISS Crewmember Demographics and Ocular Structural Changes. Crewmembers were assigned to the Folds group based on presence of peripapillary wrinkles (PPW), retinal folds (RF), or choroidal folds (CF) at any time during spaceflight. Crewmembers with no evidence of PPW, RF, or CF during spaceflight were assigned to the No Folds group. Generalized estimating equation models were used to derive marginal means and 95% confidence intervals (in brackets) for each group and difference between groups. Changes in total retinal thickness, retinal nerve fiber layer thickness, and choroid thickness were quantified as the difference between preflight (seated) and FD150, accounting for eyes nested within subjects and repeated measures over time. Two-sided P values are provided for each comparison between groups. The Benjamini-Hochberg adjusted P value is provided in parentheses when applicable. Because retinal nerve fiber layer thickness comprises a portion of total retinal thickness, these measures are not independent of each other.

	Group		**Difference between groups**	**P Value**
	No Folds	**Folds**		
Number of Crewmembers	25M / 5F	4M / 2F		
Age [Years]	46 [44 – 48]	50 [46 – 54]	4 [-1 – 9]	P = .09
BMI [kg/m^2]	25.2 [24.3 – 26.1]	27.1 [24.8 – 29.4]	1.9 [-0.5 – 4.4]	P = .12
Mission Duration [Days]	182 [161 – 202]	228 [174 – 282]	46 [-12 – 104]	P = .11
Change in TRT (BMO to 250 µm) [µm]	25.8 [19.7 – 32.0]	80.4 [33.3 – 127.5]	54.6 [7.1 – 102.1]	P = .03 (.045)
Change in RNFL Thickness (Circle Scan) [µm]	1.1 [0.0 – 1.2]	7.6 [1.7 – 13.5]	6.5 [0.6 – 12.5]	P = .03 (.045)
Change in Choroid Thickness (Circle Scan) [µm]	32.9 [25.2 – 40.6]	30.5 [11.2 – 49.7]	-2.4 [-23.2 – 18.3]	P = .81 (.81)

BMI, body mass index; TRT, total retinal thickness; BMO, Bruch’s membrane opening; RNFL, retinal nerve fiber layer thickness

FIGURE LEGENDS

Figure 1 Quantification of Bruch's Membrane Surface Roughness. Bruch's membrane surface layer was used to visualize and quantify the development choroidal folds and their progression during spaceflight. Bruch's membrane layer (red) and internal limiting membrane (blue) were manually segmented on OCT images from (A) the vertical block scan centered over the fovea and (B) the radial scan centered over the optic nerve head. Inner retinal folds (**), and choroidal folds (***) are marked on each transverse OCT image. The subtle retinal folds indicated in (A) are extensions of the prominent inner retinal folds observed in the same crewmember in Figure 2B. Bruch's membrane surface layer colored heightmap was generated to better visualize the pattern and orientation of (C) macular and (D) peripapillary choroidal folds during spaceflight: teal represents no change while dark blue and yellow represent posterior and anterior displacement respectively. The change in Bruch's membrane macular surface roughness was quantified within three adjacent 1x5 mm regions (C) to track the successive progression of choroidal folds spanning from the peripapillary region (C, Fovea – 2mm ROI) toward the fovea region (C, Fovea ROI) during spaceflight. Peripapillary surface roughness was calculated within the nasal, superior, temporal, and inferior quadrants of an elliptical region of interest within 500 to 1000 μm of Bruch's membrane opening (D).

Figure 2 Distribution of Choroidal Folds, Retinal Folds, and Peripapillary Wrinkles in ISS Crewmembers. (A) Example OCT image indicating a region of peripapillary wrinkles (*). (B) Example OCT image indicating region of inner retinal folds (**) and choroidal folds (***). In both (A) and (B) the infrared image includes the OCT scan pattern location (green lines) with the bold line representing the OCT image to the right. (C) Of the 36 participants in this study, all 6 individuals who presented with folds during spaceflight demonstrated bilateral choroidal folds. Within these 6 individuals, 8 eyes had only choroidal folds, 2 eyes had both choroidal folds and inner retinal folds, and 2 eyes had choroidal folds, inner retinal folds, and peripapillary wrinkles. (D) The prevalence of each fold type within ISS crewmember eyes demonstrating the earliest signs of optic disc edema (data presented here) differed from the prevalence of each fold type within IIH patient eyes demonstrating papilledema.[10,21] Within the 42 eyes that showed signs of developing optic disc edema during spaceflight, 2 (5%) eyes had peripapillary wrinkles, 4 (10%) had inner retinal folds, and 10 (24%) had choroidal folds. As reported in Sibony *et al.*, of 125 study eyes with papilledema, 58 (46%) eyes had peripapillary wrinkles, 59 (47%) had inner retinal folds, 25 (20%) had outer retinal folds, and 13 (10%) had choroidal folds.[10,20]

Figure 3 Progression of Macular Choroidal Folds in ISS Crewmembers During Spaceflight. Compared to preflight, macular Bruch's membrane surface roughness increases with spaceflight duration in crewmembers with macular choroidal folds. Seven study eyes from four individual crewmembers demonstrated choroidal folds in the 3 macular regions of interest (see Figure 1C for locations) during spaceflight. Each individual crewmember is represented by a different symbol shape. Open symbols represent data from the right eye and grey symbols represent data from the left eye. A meaningful increase in surface roughness was determined when the change compared to preflight exceeded a 2.3 μm threshold (shaded region).

Figure 4 Progression of Peripapillary Choroidal Folds in ISS Crewmembers During Spaceflight. Peripapillary Bruch's membrane surface roughness increased nasal, superior, and inferior to the optic nerve head, but not temporally. Average Bruch's membrane surface roughness was quantified in an annular region circumscribing the ONH within 500 μm to 1000 μm of Bruch's membrane opening. Each individual crewmember is represented by a different symbol which are consistent across figures. Open symbols represent data from the right eye and shaded symbols represent data from the left eye. A meaningful increase in surface roughness was determined when the change compared to preflight exceeded a 2.8 μm threshold (shaded region).